Corneal cross-linking versus conventional management for keratoconus: a lifetime economic model

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ABSTRACT

Aims: To assess the cost-effectiveness of corneal collagen cross-linking (CXL) versus no CXL for keratoconus in the United States (US).

Methods: A discrete-event microsimulation was developed to assess the cost-effectiveness of corneal cross-linking (CXL, Photrexa + XRL combination product) versus no CXL for patients with keratoconus. The lifetime model was conducted from a US payor perspective. The source for CXL efficacy and safety data was a 12-month randomized, open-label, sham-controlled, multi-center, pivotal trial comparing CXL versus no CXL. Other inputs were sourced from the literature. The primary outcome was the incremental cost per quality-adjusted life year gained. Costs (2019 USD) and effects were discounted 3% annually. The impacts of underlying uncertainty were evaluated by scenario, univariate, and probabilistic analyses.

Results: Starting at a mean baseline age of 31 years and considering a mixed population consisting of 80% slow-progressors and 20% fast-progressors, the CXL group was 25.9% less likely to undergo penetrating keratoplasty (PK) and spent 27.9 fewer years in advanced disease stages. CXL was dominant with lower total direct medical costs ($8,677; $30,994 versus $39,671) and more QALYs (1.88; 21.80 versus 19.93) compared to no CXL. Considering the impact of reduced productivity loss in an exploratory scenario, CXL was associated with a lifetime cost-savings of $43,759 per patient. CXL was cost-effective within 2 years and cost-saving within 4.5 years.

Limitations: Limitations include those that are common to similar pharmacoeconomic models that rely on disparate sources for inputs and extrapolation on short-term outcomes to a long-term analytical horizon.

Conclusions: Keratoconus is a progressive and life-altering disease with substantial clinical, economic, and humanistic consequences. The economic value of cross-linking is maximized when applied earlier in the disease process and/or younger age, and extends to improved work productivity, out-of-pocket costs, and quality of life.

Introduction

Keratoconus is a progressive ectasia that disrupts corneal collagen structure and causes myopia and irregular astigmatism. Patients are often affected bilaterally and asymmetrically, though unilateral disease is found in up to 4.5% of cases. Prevalence in the United States (US) and other western countries is typically cited as 55–90 cases per 100,000, but elsewhere in selected populations – particularly in the Middle East and India – is 400–2,300 per 100,000. Onset typically occurs during puberty and is initially characterized by non-specific but correctable deterioration of visual acuity: though underdiagnosis is common owing to a lack of discernible morphologic indicators during routine ophthalmological visits. While the course of the disease is variable, if left untreated, keratoconus tends to progress steadily but more rapidly in younger persons over the next 20 years. In patients with highly progressive disease, diminishing visual acuity becomes increasingly difficult to correct along with irreversible deformation and thinning of the cornea.

In its early stages, keratoconus can be managed with standard spectacles or contact lenses, but rigid contact or scleral lenses become necessary as astigmatism worsens and the cornea becomes more irregular. Eventually, in highly progressive patients, the rigid lenses can no longer be fitted and patients are left with few options other than corneal transplantation. Corneal cross-linking (CXL) is the only therapeutic option that has demonstrated efficacy in slowing or arresting the progression of keratoconus. The only CXL product approved by the US Food and Drug Administration (FDA) for the treatment of keratoconus (and corneal ectasia following refractive surgery) is a branded combination...
product, iLink1 (Photrex Viscous and Photrex 0.146% riboflavin ophthalmic solutions administered with the KXL UVA system)16. Before CXL, ectasia (including keratoconus) was the most common indication for corneal transplantation, but is now the sixth most common indication in the US. Among these procedures, penetrating keratoplasty (PK) was the most common approach (89%)19 despite the procedure being associated with relatively high rates of postoperative complications such as graft rejection, secondary glaucoma, and cataracts20,21.

Notwithstanding the demonstrated capacity of CXL for reducing the clinical burden of keratoconus1, its pharmacoeconomic impact in the US is not well-understood. Keratoconus has been identified as a costly disease with severe clinical, economic, and humanistic consequences, and treatment used to reduce or stop the progression of the disease has been found to be cost-effective5,22–24. However, no such analysis has been conducted from a US perspective to evaluate the aforementioned branded product. This analysis was conducted to evaluate the cost-effectiveness of CXL (i.e. Photrex solutions and KXL system) versus conventional treatment without CXL in patients with keratoconus in the US.

Methods

Modeling approach and patient population

A discrete-event microsimulation was developed in MS Excel to evaluate the cost-effectiveness of CXL versus conventional management without CXL for keratoconus from a US payor perspective. The primary reason for employing a patient-level microsimulation model rather than a cohort model was the need to model complex individual patient and eye histories on keratoconus progression and adjust the future risks and probabilities25.

The model individually simulated the disposition of 2,000 patients and 4,000 eyes. Baseline patient characteristics were consistent with those reported in the US multicenter clinical trials comparing CXL versus a sham control with riboflavin but without removal of the epithelium. This pivotal trial program was conducted in support of the US FDA new drug application (NDA no. 203324) for the iLink drug and device combination product that was approved by the FDA in 2016. The trials included N = 205 patients and demonstrated the effectiveness of CXL for stopping the progression of keratoconus. Key effectiveness outcomes include a decrease of 1.6 diopters for maximum keratometry and improved corrected distance visual acuity of 5.7 logMAR units observed over 12 months1.

In the present model, patients diagnosed with bilateral progressive keratoconus had a base case mean age of 31 years, consistent with the CXL pivotal trial used as the primary source of clinical inputs for this model1. Individual eyes were then modeled with the patient him/herself over the remaining lifetime. Background mortality was applied using actuarial life-tables26. Refer to Figure 1 for a schematic of the overall model structure, the components of which are described in subsequent sections.

Initial disposition and treatment

As a first step in the model, patients either received CXL or did not. The initial settings for eye curvature (maximum keratometry on the Scheimpflug system) and corrected distance visual acuity for the better of the two eyes were drawn from the reported distributions of the baseline measurements reported in the pivotal clinical trial1 (Table 1). The other eye was set to 90% severity of the better eye (i.e. 10% worse). This assumption was derived from the study by Jiménez-García et al. on the basis of the regression equation relating the relative severity of the best eye versus the worst eye at...
baseline with respect to curvature. Consistent with the clinical literature and previous economic models in keratoconus, it was assumed that the disease is bilateral in all patients.

The initial disease stage of each eye was based on the dioptric component of the Amsler-Krumeich (AK) classification, which has been used in a similar economic model. The AK classification for keratoconus has four stages ranging from least severe (stage 1) to most severe (stage 4). Patients with keratoconus can be broadly categorized as "fast-progressors" (those with an initial rapid disease progression) and "slow-progressors" (those with an initial slow disease progression) on the basis of $K_{\text{Max}}$ (diopter). In both groups (fast and slow progressors), the rate of progression is expected to decrease with age. Our base case analysis therefore included both types of patients whereby the baseline rate of increase (i.e. worsening) of $K_{\text{Max}}$ was 0.021 D per year for slow progressors and of slow-progressors and fast-progressors worsened (increased) at the previously observed rate of 0.021 diopters and 0.228 diopters per year, respectively. It has also been observed that the "slow-progressors" outnumber "fast-progressors", but the precise proportions are not well-established. Based on our clinical experience and consistent with information from the literature, proportion of slow progressors was 80% and the proportion of fast progressors was 20% the ratio of slow-progressors to fast-progressors was set to 4:1.

### Disease progression

Disease progression was modeled on the basis of AK classification according to the degree of curvature ($K_{\text{Max}}$). Curvature was modeled over time for each eye independently according to annualized rates reported previously (Table 2). Rates reported in Table 2 are the baseline rates of progression for the worse eye, but (consistent with previous observations) progression diminished with increasing age in both "slow" and "fast" progressing groups. Disease progression in the better eye was determined by applying to these values the relative severity coefficient described above.

### Risk of penetrating keratoplasty

The risk of PK was evaluated on the basis of four variables: age, comfort, best corrected visual acuity (BCVA), and curvature ($K_{\text{Max}}$) and was modeled separately for patients with and without spectacles as baseline. In the previous model by Rebenitsch et al., these variables populated a logistic equation used to determine the probability of PK in any given model cycle. As the present analysis was a discrete event simulation without model cycles, this logistic equation was converted to a time-to-event analysis as follows:

**Step 1:** We began with the equation used by Rebenitsch et al. (originally based on Gordon et al.) that was used in the logistic regression to predict probability of PK:

$$P(x) = \frac{1}{1 + e^{-(x + \sum \beta_i \chi_i)}}$$

**Step 2:** We solved the equation for $(x + \sum \beta_i \chi_i)$ so that we could evaluate time as a function of probability instead of probability as a function of time, yielding the following:

$$\alpha + \sum \beta_i \chi_i = -\ln \left( \frac{1 - P(x)}{P(x)} \right)$$

**Step 3:** We substituted in the following parameter estimates and functions (sourced from Rebenitsch and derived originally from Gordon et al.) where $\alpha$ is the intercept estimate, and $\beta_i$ represents each of the other parameter estimates. $\chi_i$ represents the equation corresponding to the parameter estimate (e.g. if $\beta_i$ is the BCVA, then $\chi_i$ would be the equation for best corrected visual over time (baseline score + rate of change × time)).

The following functions represent the $\chi_i$ for each parameter, with the baseline and change values coming from the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study:

- BCVA = 52.9 - 0.117t;
- Curvature $= 46.6 + 0.207t$
- Change in curvature $= 0.228$ (fast-progressors) or $0.021$ (slow-progressors);
- Change in BCVA $= -0.119$;
- Comfort $= 2.4 - 0.023t$.

**Step 4:** After all substitutions, we solved the equation to get time on one side and probability as well as all other constants on the other side. This resulting equation produced time to PK as a function of probability randomly drawn from between 0 and 1 for each event/patient.

**Costs and utilities**

Costs and utilities were based on values reported in the literature and are listed in Tables 2 and 3. The direct medical costs of PK were estimated using a 2013 report by the Eye Bank Association of America. The report details an analysis conducted to assess the total and component costs of three types of keratoplasty (lamellar, penetrating, and endothelial) conducted in the US healthcare setting using claims data and reimbursed amounts. The costs of corrective lenses were stratified by two categories: “less severe” applied to AK stages 1 and 2 and “more severe” applied to AK stages 3 and 4. Adverse event costs were applied for the CXL procedure and PK procedure separately. While both procedures are associated with a variety low-probability adverse events, the clinical ophthalmologist authors of this report (RLL, JPB, EDD, VT) identified which among these should be included in the model due to their clinical significance. All adverse events were applied on a one-off, per event basis and include the costs attributable to clinically attending each for up to 1 year (i.e. the maximum considered time horizon for a given adverse event).

Utilities applied to AK health states were not available from the CXL clinical trial and were instead extracted from Salmon et al. who applied time-trade-off regression models to derive utilities largely on the basis of visual acuity. All costs are reported in 2019 US dollars. When necessary, costs were adjusted to 2019 US dollars using the medical care component of the US Bureau of Labor Statistics Consumer Price Index for all urban consumers.

The impact of CXL versus no CXL on work productivity was assessed in a scenario analysis by taking the product of the estimated proportion of work missed by AK stage and the average annual wage in the US in the year 2019 (i.e. $42,000). Based on author assumptions, it was assumed that 0%, 2%, 3%, and 5% of patients in AK stages 1, 2, 3, and 4, respectively, could not work at all due to their keratoconus disease. Further, it was assumed that 1%, 3%, 5%, and 10% in AK stages 1, 2, 3, and 4, respectively, had a 10% reduction in work productivity. Due to the highly speculative nature of these assumptions, this stand-alone scenario was not part of the base case or other scenario or sensitivity analyses.

**Base case analysis**

In the base case, 1,000 patients (2,000 eyes) were simulated per treatment arm and only direct medical costs were included. This sample size was chosen based on the point at which variability in the ICER outcome was determined by

| Table 3. Resource utilization, costs, and (dis)utilities. |
|--------------------------------------------------------|
| **Procedures (per eye)**                                |
| Penetrating keratoplasty $\text{\$22,165}$ Eye Bank Report 2013$^\text{37}$ |
| Cross-linking $\text{\$4,630}$ Sum of parts |
| Procedure cost$^a$ $\text{\$1,780}$ CMS.Gov |
| Photorexa cost $\text{\$2,850}$ Micromedex for Q1 2020 |
| **Spectacles/lenses and routine eye exams**             |
| Glasses $\text{\$356}$ $^\text{37}$ |
| Lenses (less severe)$^b$ $\text{\$400}$ Avg. annual cost from constituent lens types |
| Lenses (more severe)$^c$ $\text{\$800}$ Avg. annual cost from constituent lens types |
| Lens fitting$^a$ $\text{\$362}$ CMS.Gov |
| Routine check-up$^a$ $\text{\$362}$ CMS.Gov |
| **Adverse events (annual or event)**                    |
| Rise in IOP $\text{\$46}$ $^\text{22}$ |
| Graft rejection $\text{\$604}$ $^\text{22}$ |
| Glaucoma $\text{\$3,629}$ $^\text{38}$ |
| Enucleation $\text{\$3,386}$ $^\text{39}$ |
| Other$^d$ $\text{\$862}$ $^\text{Avg. cost based on constituent AEs}$ |
| **Utilities and disutilities**                          |
| AK stage 1 $\text{0.852}$ $^\text{23}$ |
| AK stage 2 $\text{0.800}$ $^\text{23}$ |
| AK stage 3 $\text{0.770}$ $^\text{23}$ |
| AK stage 4 $\text{0.749}$ $^\text{23}$ |
| Graft rejection $\text{-0.150 (6 months)}$ $^\text{24}$, duration assumed |
| Raised IOP $\text{-0.001 (3 months)}$ $^\text{Assumption}$ |
| Glaucoma $\text{-0.100 (2 months)}$ $^\text{24}$, duration assumed |
| Enucleation $\text{-0.300 (0–24 months)}$ $^\text{35}$, duration assumed |
| Enucleation $\text{-0.100 (24 months to death)}$ $^\text{35}$, duration assumed |

$^a$Nationally representative value from a private payor perspective was not available and so the value from CMS/Medicare was used.

$^b$Includes a mixture of the following types of lenses: soft toric, custom soft toric.

$^c$Includes a mixture of the following types of lenses: piggyback (soft + RGP), hybrid, scleral.

$^d$Includes a mixture of the following events: cataracts, infection, other irritation.
visual inspection to be within acceptable limits. This occurred at \( N = 1,500 \), and so \( N = 2,000 \) was considered a safe assumption. The model was programmed such that the baseline characteristics were identical between treatment groups. The incremental cost-effectiveness ratio (ICER) for CXL versus no CXL was calculated as the difference in total costs divided by the difference in QALYs between the two groups. Consistent with the most recent guidance pertaining to the US, an ICER \( \leq $150,000 \) per QALY was considered cost effective and outcomes (costs and QALYs) were discounted at 3.0% annually.

### Scenario and sensitivity analysis

A number of scenario analyses were used to assess the impact of CXL versus no CXL beyond the more conservative limits of the base case.

In scenario 1, we evaluated the impact of CXL versus no CXL on lost work productivity by applying assumptions regarding the proportion of work missed in each AK stage. In scenario 2, we evaluated the drug acquisition cost of the PhotrexA component of the CXL combination product at which cost-neutrality was reached and at which the upper limit of cost-effectiveness was reached. In scenario 3, we evaluated the relationship between baseline age and the modeled endpoints by running the model at mean baseline ages of 10, 20, 30, and 40 years. Rather than applying the mixed cohort approach from the base case, the rate of change of \( k_{\text{Max}} \) by baseline age reported by Ferdi et al. was inputted into the model for the respective ages.

Lastly, a key characteristic of the base case scenario is that keratoconus progressed until death. Though it progressed extremely slowly above age 45 years due to the attenuating impact of age, the potential for lifelong progression (which again was extremely minimal in advanced ages) could have some impact on the outcomes. Some clinical evidence suggests that progression for many patients might effectively stop at approximately age 45 years \(^{36,42} \). Thus, in scenario 4, we assumed progression diminished with age (as in the base case) but also that progression stopped at age 45 years.

To account for uncertainty inherent in the input values, we conducted one-way univariate and probabilistic sensitivity analysis. The distributions of parameters were based on either the original data source or some assumptions according to the type of variables. Unless specified otherwise, the gamma distribution was used for costs, the beta distribution was used for probabilities and (dis)utilities, and the uniform distribution was used for durations. A Dirichlet distribution was applied in cases where a correlation structure should be maintained (e.g. where multiple probabilities must add to 100%). Where not reported in the source material, the standard deviation for a given input value was varied \( \pm 20\% \). For probabilistic sensitivity analysis, we ran 1,000 simulations, each including 2,000 patients and 4,000 eyes; the model parameters for these estimates were randomly drawn based on the aforementioned distributions. The results are shown as an incremental cost-effectiveness scatterplot with a 95% confidence ellipse.

### Results

#### Base case

We simulated outcomes for 2,000 patients (4,000 eyes) individually with a mean starting age of 31.1 years over a mean follow-up of 52.3 years (i.e. reflecting an average age of death of 83 years) and assuming a 4:1 ratio of slow to fast progressors. Among the overall patient population, CXL patients underwent fewer PKs (~25.9%; 1.0% versus 26.9%) and spent less time in the more severe AK stages 3 and 4 (~27.9 years; 1.8 years versus 29.8 years). In the slow-progressing subgroup 0.3% in the CXL arm and 8.7% in the no CXL arm underwent PK, while in the fast-progressing subgroup 2.5% in the CXL arm and 92.7% in the no CXL subgroup underwent PK. Similar trends were observed for time spent in AK stages.

Considering the overall patient population across a lifetime horizon, CXL was the dominant treatment strategy as it was associated with lower total direct medical costs (~$8,677; $30,994 versus $39,671) and more QALYs (1.88; 21.80 versus 19.93) compared to conventional treatment without CXL (Figure 2). Among slow-progressors, CXL was associated with higher direct medical costs ($2,612; $30,667 versus $28,055) and more QALYs (1.71; 21.80 versus 20.10). The resultant ICER was cost-effective at $1,526 per QALY gained against a maximum willingness-to-pay of $150,000 per QALY gained. CXL was dominant among fast-progressors given the lower direct medical costs (~$53,832; $32,300 versus $86,133) and higher QALYs (2.55; 21.80 versus 19.20) (Figure 2).

#### Sensitivity analysis

The one-way univariate sensitivity analysis (Figure 3) indicated that the outcomes were most sensitive to the ratio of slow-progressors to fast-progressors, the cost of PK, and utility values for AK stages. The probabilistic analysis (Figure 4) indicated that the model was robust to underlying input uncertainty with a 96% probability of CXL being dominant. A somewhat horizontal pattern for the model replicates was observed partly due to the scaling of the graph, but is also attributable (as has been observed elsewhere\(^ {23} \)) to a lack of variability for input costs.

#### Alternative scenarios

In an alternative scenario, we assumed that disease progression stopped after age 45 (in addition to the assumption that the rate of disease progression lessens with advancing age). This scenario had a small impact on the outcomes in that it reduced – over a lifetime horizon – the cost savings by $1,400 and decreased the QALYs gained by 0.04.

Threshold analysis was conducted to evaluate the acquisition cost of PhotrexA (the pharmaceutical component of the branded CXL combination product) at which cost neutrality...
Figure 2. Economic outcomes for subgroups and overall.

Figure 3. Univariate sensitivity analysis for base case (varied ±20%).
is reached. From this context, CXL remains cost-neutral with an acquisition cost of Photrex of up to $5,763 per eye, and remains cost-effective until an acquisition cost of up to $12,985.

In the exploratory analysis, conducted to estimate the impact of disease progression on work productivity, CXL was associated with a reduction in lifetime cost (including lost productivity) of $43,759 and a reduction in out-of-pocket costs of $4,248 over a lifetime. The outcomes of the exploratory analysis where the mean baseline age was varied from age 10 to age 40 are presented in Figure 5 and demonstrate a strong relationship between lower baseline age and greater lifetime benefits of CXL.

**Discussion**

We used a microsimulation model to evaluate the costs and effects of CXL treatment for keratoconus versus conventional management without CXL among patients with a mean baseline age of 31 years, consistent with the characteristics of the iLink CXL pivotal trial. This base-case scenario yielded lower direct medical costs and more QALYs for the CXL group. From a US national context where prevalence is at least 55 keratoconus cases per 100,000 among a total general population of 330 MM4,43, the lifetime cost-savings (including direct medical costs and lost-productivity) of $43,759 over a person’s lifetime lasting 52.3 years from the model baseline would equate to a national savings of $150 MM per year. The aforementioned prevalence observed in the year 1986 is commonly cited but is likely an underestimate given the advent of more precise diagnostic methods29, which suggests that the national cost-savings implications for CXL could be higher. For example, if applying the prevalence reported by Godefrooij et al. for the Netherlands5 (i.e. 266.7 cases per 100,000 general population) to the US, the annual national cost savings associated with CXL would be $736 MM. The prevalence value used to generate this estimate could be an overestimate, but it is
unique among others because it uses more contemporary diagnostic technologies and so offers an important juxtaposition compared to the earlier estimate generated with the prevalence value reported in Kennedy et al.4

Scenario analyses where the baseline age was increased in 10-year increments (Figure 5) indicated that the pharmacoeconomic benefits of CXL were negatively associated with baseline age such that these benefits decreased as patients’ age at the time of CXL increased. In one-way univariate sensitivity analysis, the model was most sensitive to the ratio of fast- to slow-progressing patients and second to the cost of PK. The probabilistic sensitivity analysis demonstrated that the underlying uncertainty in model inputs had little impact on the overall outcomes whereby 96% of the model runs produced a situation where CXL was dominant over no CXL.

Given that the target indication for this model is one where individual patient histories are complex, varied, and have a meaningful impact on clinical outcomes, our application of a discrete event microsimulation was in our judgment the most precise and comprehensive modeling approach possible. For example, the lifetime risk of PK across all patients was consistent with previous reports.35 Other strengths of this analysis include input from clinical ophthalmologists actively treating keratoconus and the separate modeling of each eye to reflect the disease burden more precisely.

The optimal application of health state utility values within ophthalmologic models is the subject of a long debate focusing primarily on two issues: (1) whether utility should be based on the best- or worst-seeing eye and (2) whether utility should be based on a single index (e.g. visual acuity or curvature) or if it should be based on a composite of measurements (e.g. AK classification). This analysis was a two-eye model in which one’s utility was based on the AK stage of the better eye. By taking this approach, we were consistent with the literature supporting best-eye based utility attribution and with the literature supporting the use of utility estimations elicited through time-trade-off.

This model also considers the impact of lost work productivity, which is known to have a meaningful impact on persons with keratoconus.33 Previous models have been limited in that they did not evaluate this source of economic impact.22-24,52 It should be noted that the humanistic burden of keratoconus (and the extent to which this can be alleviated by CXL) is partly captured by the utility values ascribed to the AK health states and by extension the QALYs gained. It was further captured in the present analysis by two exploratory analyses: one that assumed a up to 70% of lens and CXL costs are out-of-pocket expenses for the patient, and another that evaluated the potential impact of CXL on lost productivity.

Table 4 summarizes key characteristics and outcomes of the present model versus previously published cost-effectiveness analyses. In each instance, CXL is cost-effective, but the present model is unique in being the only one where CXL is dominant. This is primarily driven by two considerations. First, the other economic analyses were conducted from ex-US perspectives where healthcare costs are much lower, and it is particularly important to consider the ratio of the cost of the technology of interest (i.e. CXL) relative to the cost of what the technology is intended to prevent (i.e. PK). In our US-based analysis, the per eye costs of CXL and PK were $4,630 and $22,165, respectively (i.e. 1:5 ratio). Elsewhere this ratio is lower (e.g. in Salmon et al., the ratio is 1:2 (i.e. £928: £1,766)). As CXL is preventing an event that is much more expensive in the US, it follows that the present analysis would demonstrate cost-savings where not observed elsewhere. The present analysis also demonstrated larger QALY gains versus what was observed in the other economic analyses. This is partly due to higher discounting rates used in most ex-US analyses (e.g. 5.0% in Leung et al.24 versus 3.0% here), and because the ex-US analyses having applied higher probabilities of CXL failure, which limited the potential QALY gains for CXL. Perhaps more impactful was an assumption employed in other analyses that patients who underwent PK would automatically have a considerable rebound in utility (e.g. in Salmon et al. utility could improve from 0.75 to 0.87 after PK23). The present analysis was more conservative in this regard by requiring that a PK would need to generate an improvement in AK stage in order for utility to improve. This occurred fairly regularly, but the utility differences between AK stages in the present analysis were not as large as the utility improvements due to PK conferred elsewhere.

It is also important to note that the present model set the cost of lenses at their current values (i.e. as of the year 2019) and then conservatively applied a discount to these costs over time. In reality, trends in the US suggest that specialty lens costs will likely increase over time due to advancing technology and the entry of new branded products into the market. Had this observation been implemented in this model, the pharmacoeconomic benefits of CXL would have increased due to the demonstrated capacity of CXL to reduce time spent in more advanced disease stages that are associated with more expensive lenses.

Table 4. Summary of economic models evaluating CXL for keratoconus.

| Country  | Present analysis | Salmon 2015 | Godefrooij 2017 | Leung 2017 |
|----------|-----------------|------------|----------------|------------|
| Horizon  | US | UK | Netherlands | Canada |
| Comparator | Lifetime | 25 years | Lifetime | Lifetime |
| CXL stabilizing effect | Conventional | Conventional | Conventional | Conventional |
| Type | Microsimulation | 92% at year 5 | Cohort | Microsimulation |
| Discount | 3.0% | 3.5% | 3.0% | 5.0% |
| Base age (years) | 31 | 21 | 22 | 25 |
| Lifetime cost diff. | $5,677 | $0.051 | $3,004 | $0.33 |
| QALYs gained | 1.88 | NR | NR | NR |
| ICER | Dominant | £3,174 | £54,384 | £9,090 |
**Limitations**

This analysis includes important limitations. First, the clinical effectiveness for CXL was based on a Phase 3 clinical trial comparing CXL with conventional management without CXL, but PK was not the comparator specifically. Therefore, the comparison of CXL versus PK was carried out on a naive basis because the analysis did not include relative clinical impacts evaluated directly between the two treatment pathways. This limitation was unlikely to have a meaningful impact on the modeled results given the relative stability of our outcomes when varying clinical effectiveness parameters. Furthermore, we did not have access to the original patient-level data from the CXL clinical trial reported by Hersh et al., and so could not evaluate and apply a correlation structure among baseline characteristics during our initial sampling procedure. The resulting assumption, that the baseline characteristics were uncorrelated, is a likely oversimplification; although, our approach is consistent with the other published microsimulation models in keratoconus that also appear to have been limited by a lack of access to underlying patient-level data.

Second, as has been cited as a limitation in previous economic models in keratoconus, the present analysis used short-term (i.e. 12-month) effectiveness outcomes for CXL to extrapolate long-term effects; particularly as they relate to the durability of the initial treatment effect. While the disease-attenuating effect of CXL may diminish over time, our clinical experience indicates an exceedingly low long-term CXL failure rate (i.e. consensus of ≤1% failure rate); although long-term outcomes for the KXL System and Photrexa combination product used for the iLink procedure specifically are unknown. Nonetheless, this analysis incorporated a base case CXL failure rate of 1% by year 10, which was varied to as high as 6% in sensitivity analysis based on reports from the clinical literature. The findings were not impacted meaningfully, likely due to the comparatively higher lifetime probability of PK failure, which has been observed to be as high as 97%.

Third, as was the case in the only previous economic analysis of keratoconus from a US payer perspective, the present model relied on precedent in the literature to evaluate the relationships among parameters of the disease (e.g. visual acuity, curvature, and comfort), patient age, and time. Many of these relationships were originally based on older studies (prominently the CLEK study) that might not reflect the current treatment landscape and overall disease profile for keratoconus as it relates to patient age. Due to the availability of CXL, for example, the study design employed in CLEK would be untenable today.

Lastly, a key driver of model outcomes was a variable for which evidence is minimal: the ratio of slow-progressing to fast-progressing patients. Here, this ratio was set to 4:1 based primarily on a previous observation that keratoconus progresses quickly in 20–25% of patients with mild-moderate disease. This assumption is consistent with the findings of the landmark CLEK study, in which a similar proportion of patients were shown to progress as a higher rate than the overall keratoconus population (24% of patients progressed by 3.00 D increase in curvature over an 8 year period, an average of 0.38 D per year). Given that keratoconus traditionally progresses more quickly in younger patients combined with the potential for underdiagnosis of keratoconus among young persons who we have observed in our clinical experience and that is substantiated by the more advanced stage of keratoconus at time of diagnosis in pediatric patients as compared to adults, it is possible that the applied ratio underestimates the proportion of fast-progressors in the overall keratoconus population. Thus, our analysis may be somewhat conservative given the benefits of CXL are greater in the fast-progressing subgroup (Figure 2).

**Conclusions**

CXL is associated with lower costs and better clinical outcomes when used to treat keratoconus versus conventional management without CXL. These benefits were driven primarily by the ability of CXL to reduce the incidence of costly PK procedures that may occur as keratoconus progresses and might otherwise impart considerable burden. Furthermore, benefits of CXL are maximized among younger patients such that the earlier a person with keratoconus undergoes CXL, the more clinical and economic benefits that will accrue.

**Note**

i. iLink is a registered trademark of Glaukos Corporation, San Clemente, CA, USA.

**Transparency**

**Declaration of funding**

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**Declaration of financial/other relationships**

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