• Clinical Research •

Efficacy and safety of progressive fluence pulsed light epithelium-on accelerated corneal cross-linking for progressive keratoconus: 18-month prospective results

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Abstract

● **AIM:** To report the 18-month clinical outcomes of the progressively higher fluence pulsed light (7.2 to 10 J/cm^2) epithelium-on accelerated corneal crosslinking (PFPL M Epi-On ACXL) protocol for progressive keratoconus.

● **METHODS:** This was a prospective, non-randomized interventional study. Fluence was assigned based on preoperative pachymetry: 7.2 J/cm^2 (≤420 μm), 8.6 J/cm^2 (420–459 μm), or 10 J/cm^2 (≥460 μm). Riboflavin solutions (Paracel I and II), pulsed ultraviolet-A (UVA) irradiation (1s on/off), and consistent procedural timing (13min irradiation) were applied using the KXL I system. Uncorrected and best-corrected distance visual acuity (UDVA, CDVA), maximum keratometry (Kmax), higher-order aberrations (HOAs), and anterior segment optical coherence tomography (OCT) demarcation line depth were analyzed at baseline, 6, 12, and 18mo.

● **RESULTS:** Totally 32 eyes of 32 patients aged over 26y with progressive keratoconus underwent PFPL M Epi-On ACXL were included. All groups demonstrated long-term stability in UDVA and CDVA. The 10 J/cm^2 group showed the greatest improvement in CDVA (+0.17 decimal), significant corneal flattening (Kmax reduction: −1.03 D), and the most substantial HOAs reduction (−0.30 μm). No significant differences were observed between the 7.2 and 8.6 J/cm^2 groups. OCT showed fluence-dependent demarcation line depths: 250±30 μm in the 10 J/cm^2 group. No adverse events were observed.

● **CONCUSION:** PFPL M Epi-On ACXL appears to be a safe, repeatable, and effective long-term treatment for progressive keratoconus. The 10 J/cm^2 fluence is associated with better optical and structural outcomes compared with lower fluences. Consistency in protocol application is essential to ensure efficacy.

● **KEYWORDS:** epithelium-on corneal crosslinking; transepithelial crosslinking; higher-fluence crosslinking; corneal ectasia; keratoconus

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INTRODUCTION

Keratoconus (KC) is a progressive, ectatic disorder of the cornea, often manifesting in the second and third decades of life. It leads to progressive stromal thinning, corneal steepening, and visual impairment. Emerging evidence supports a chronic inflammatory component in KC pathogenesis[1-3].

Riboflavin/ultraviolet-A (UVA) corneal crosslinking (CXL) with epithelium removal (Epi-Off CXL) is currently the gold standard treatment for progressive KC due to its well-demonstrated efficacy in halting ectasia and improving biomechanical stability[4]. However, the procedure is associated with risks such as pain, infection, and delayed recovery[5]. Rarely, haze may develop months later and persist, impairing vision[6].

Epithelium-on (Epi-On) CXL, while offering the advantage of reduced morbidity and faster visual recovery, initially lacked sufficient efficacy due to limited stromal riboflavin diffusion and oxygen availability[7]. Recent advances—including enhanced riboflavin formulations, increased UVA fluence, and pulsed-light delivery—have shown promise in improving the depth and biomechanical impact of Epi-On CXL[8].

The present study builds upon these innovations by investigating the long-term clinical outcomes of a pachymetry-based, progressively higher fluence pulsed light Epi-On accelerated CXL (PFPL M Epi-On ACXL) protocol. This technique employs three distinct fluence levels (7.2, 8.6, and 10.0 J/cm^2) based on corneal thickness, combined with a consistent application protocol to enhance both safety and efficacy[9]. We report the 18-month prospective outcomes from this novel approach.

PARTICIPANTS AND METHODS

Ethical Approval The study was conducted under the same Institutional Review Board approval of the Siena Crosslinking Center (Code: PFPL.EPION 2.0), in accordance with the tenets of the Declaration of Helsinki. Ethical approval was obtained prior to study initiation. A control or sham group was not permitted by the Institutional Review Board due to ethical concerns related to untreated progressive KC. No new patients were enrolled, and no additional interventions were performed beyond the original PFPL M Epi-On Accelerated CXL protocol, which was already approved and published. Therefore, the present work represents a prospective longitudinal follow-up of an already institutional review board approved cohort rather than a newly initiated clinical trial, and it was not registered separately in a clinical trial registry.

This was a prospective, open-label, non-randomized interventional study including 32 eyes of 32 patients aged over 26y, diagnosed with stage I–III progressive KC. Inclusion criteria included a minimum corneal thickness of 400 μm, documented disease progression [≥1.0 D increase in maximum keratometry (Kmax), ≥10 μm thinning, or ≥0.1 decimal loss of uncorrected or best-corrected distance visual acuity (UDVA/CDVA) in the previous 6mo], and no previous ocular surgery, herpetic keratitis, or autoimmune disorders.

Patients were stratified into three groups according to baseline pachymetry: Group 1: ≤420 μm, 7.2 J/cm^2 (n=10); Group 2: 420–459 μm, 8.6 J/cm^2 (n=11); Group 3: ≥460 μm, 10.0 J/cm^2 (n=11).

All procedures were performed under topical anesthesia (0.4% oxybuprocaine) using a standardized protocol. Riboflavin loading consisted of Paracel I [0.25%, hydroxypropyl methyl cellulose (HPMC)-based] for 4min, followed by Paracel II (0.22%, saline-based) for 6min. Irradiation was performed using the Glaukos KXL I device in pulsed mode (1s on/off) for 13min. UVA irradiation was performed using the Glaukos KXL I device in pulsed mode (1s on/off) for a constant total exposure time of 13min. UVA intensity was adjusted to achieve the desired total fluence (7.2, 8.6, or 10 J/cm^2), corresponding to intensities ranging from 18 to 26 mW/cm^2. The ratio between fluence (J/cm^2) and intensity (mW/cm^2) followed the standard physical relation $F=I\times t$ (where t represents the effective on-time), according to the methodology previously developed and validated by our group[9]. This approach ensured precise calibration of photonic energy delivery and reproducibility of the PFPL M Epi-On ACXL protocol.

Postoperative treatment included non-steroidal anti-inflammatory drug (NSAID) drops and oral analgesics for 24h, followed by tapered topical steroids (fluorometholone 0.2%) and lubricants for 6wk. Follow-up examinations were conducted at baseline, 1, 3, 6, 12, and 18mo, including UDVA, CDVA, Kmax, higher-order aberrations (HOAs), minimum central corneal thickness (CCT), and optical coherence tomography (OCT) imaging of the demarcation line (DL). Endothelial counts were measured pre- and postoperatively. Although interim visits at 1, 3, and 12mo were performed, the present analysis focuses on clinically meaningful mid- and long-term outcomes.

This 18-month follow-up report refers to the same cohort of 32 eyes of 32 young-adult patients with Stage I–III progressive KC previously described in our earlier publication[9]. The riboflavin formulations used (Paracel parts 1 and 2, Glaukos-Avedro, Burlington, USA) and the fluence settings (5.4–15 J/cm^2) had been previously validated and published as safe in both Epi-Off and Epi-On accelerated customized CXL procedures.

RESULTS

A total of 32 eyes from 32 patients (male/female: 28/4, mean age: 29.4±1.4y, range 27–32y) were analyzed. No intraoperative or postoperative complications were reported. Visual acuity outcomes showed stability or improvement across all fluence groups. All 32 eyes (32 patients) completed the full 18-month follow-up, with no cases of loss to follow-up or protocol deviation.

Figure 1 illustrates the progressive reduction in HOAs across all treatment groups, with the most substantial improvement seen in the 10.0 J/cm² group.

Figure 2 shows a representative anterior segment OCT image of the DL observed 15d after 10.0 J/cm² EFPL M Epi-On ACXL. DL depth on OCT was: 211±19 μm in Group 1, 245±23 μm in Group 2, and 267±21 μm in Group 3. Table 1 shows the depth of DL expressed as a percentage of the minimum CCT. Table 2 shows CCT at baseline, 6, and 8mo across different fluence groups.

Representative corneal tomography illustrating topographic flattening after 10.0 J/cm² EFPL M Epi-On ACXL is shown in Figure 3. Based on Kmax variation, the percentage of eyes demonstrating corneal flattening (≥0.5 D reduction), stability (±0.5 D), or worsening (≥0.5 D increase) was as follows: Group 1 (7.2 J/cm^2): 7/10 eyes (70%) flattened, 3/10 (30%) stable, none worsened. Group 2 (8.6 J/cm^2): 6/11 eyes (55%) flattened, 5/11 (45%) stable, none worsened. Group 3 (10.0 J/cm^2): 9/11 eyes (82%) flattened, 2/11 (18%) stable, none worsened.

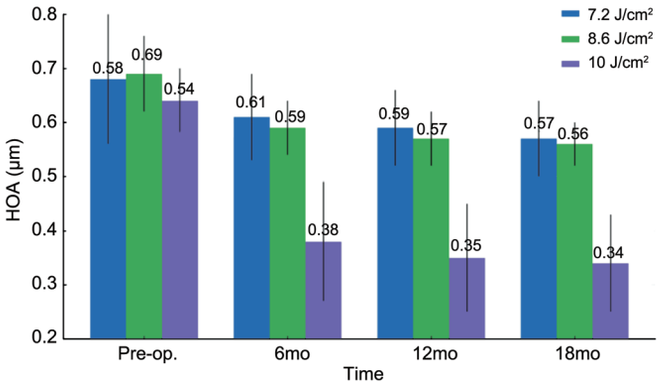

Figure 1 Higher order aberrations (HOA) at baseline, 6, 12, and 18mo.

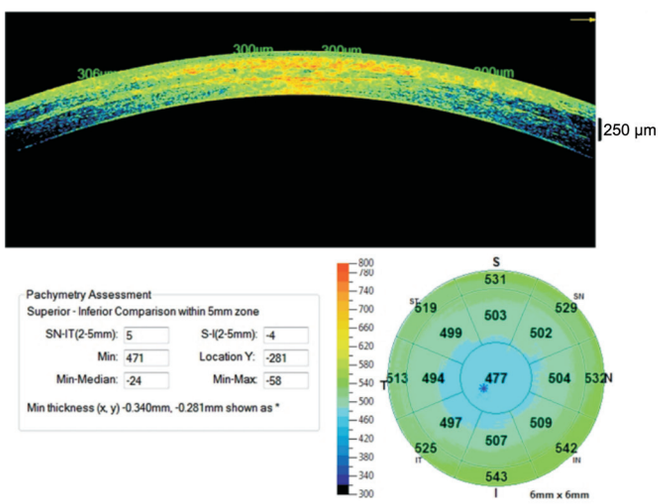

Figure 2 Anterior segment optical coherence tomography (OCT) image showing the stromal demarcation line 15d after 10.0 J/cm² enhanced fluence pulsed light (EFPL) M Epi-On accelerated cross-linking (ACXL) The interface appears as a distinct hyperreflective line. Scale bar=250 μm.

Statistical analysis confirmed a significant improvement in key clinical parameters in the 10.0 J/cm² group. Kmax decreased by −1.03 D (P<0.0001). HOA decreased by −0.30 μm (P<0.0001). CDVA improved by +0.17 decimal units (P<0.0001). In the 7.2 J/cm² group, the improvement in Kmax (P=0.0029), HOA (P=0.0023), and CDVA (P=0.0001) was also statistically significant, though of smaller magnitude. The 8.6 J/cm² group showed borderline significance for Kmax (P=0.0355) and HOA (P=0.0009), while the change in CDVA did not reach statistical significance (P=0.0706; Table 3).

Endothelial cell density (ECD) remained stable throughout the follow-up period in all treatment groups. Mean preoperative ECD values were 2650±148 cells/mm² in Group 1 (7.2 J/cm²), 2683±132 cells/mm² in Group 2 (8.6 J/cm²), and 2702±141 cells/mm² in Group 3 (10.0 J/cm²). At 6mo, values were 2639±146, 2675±128, and 2695±137 cells/mm², respectively. At 18mo, ECD values remained virtually unchanged: 2632±144 cells/mm² (Group 1), 2668±130 cells/mm² (Group 2), and 2690±134 cells/mm² (Group 3). No statistically significant differences were observed compared to baseline

Table 1 Depth of DL expressed as a percentage of the minimum CCT

Group	DL/minimum CCT (μm)	DL (% of minimum CCT)
Group 1	211/400	52.75%
Group 2	245/420	58.33%
Group 3	267/460	58.04%

DL: Demarcation line; CCT: Central corneal thickness.

Table 2 CCT at different fluence groups mean±SD, μm

Groups	Baseline	6mo	18mo
Group 1 (7.2 J/cm²)	405±12	411±15	416±14
Group 2 (8.6 J/cm²)	437±10	441±17	439±12
Group 3 (10.0 J/cm²)	472±15	473±13	479±11

SD: Standard deviation; CCT: Central corneal thickness.

(P>0.05 for all comparisons), and no cases of endothelial decompensation or corneal edema were reported.

DISCUSSION

The results of this 18-month prospective study validate the safety and efficacy of the PFPL M Epi-On ACXL protocol in stabilizing progressive KC, particularly when fluence is modulated according to corneal pachymetry. This customized approach to fluence delivery—7.2, 8.6, and 10.0 J/cm²—demonstrated predictable and consistent outcomes, with no recorded intraoperative or postoperative complications.

The 10.0 J/cm² group exhibited the most marked improvements in visual acuity, corneal flattening (Kmax reduction), and HOA reduction. Specifically, a mean CDVA gain of +0.17 decimal equivalents and a Kmax decrease of −1.03 D confirm the structural and functional impact of this high-fluence strategy. Importantly, the DL depth reached an average of 267±21 μm in this group, reinforcing the correlation between fluence and crosslinking penetration. These findings are consistent with prior experimental and clinical observations that increased fluence levels enhance the biomechanical stiffening of the cornea[10-11].

Conversely, the 7.2 and 8.6 J/cm² groups showed similar trends in stabilization but did not yield statistically significant improvements in Kmax or HOA reduction. This outcome reinforces the concept that while Epi-On protocols can be safe and effective in thinner corneas[12], their efficacy may be fluence-dependent and limited in biomechanical reach when lower energy levels are used[8]. The significant reduction in Kmax and HOA, coupled with improved CDVA, particularly in the 10.0 J/cm² group (P<0.0001 across all metrics), supports the hypothesis that higher fluence enhances biomechanical and functional outcomes in Epi-On CXL. While the 7.2 and 8.6 J/cm² protocols also demonstrated statistically significant improvements in Kmax and HOA, their impact on visual acuity was more modest and less consistent (P=0.0706 for CDVA in the 8.6 J/cm² group).

These results underscore the fluence-dependent nature of

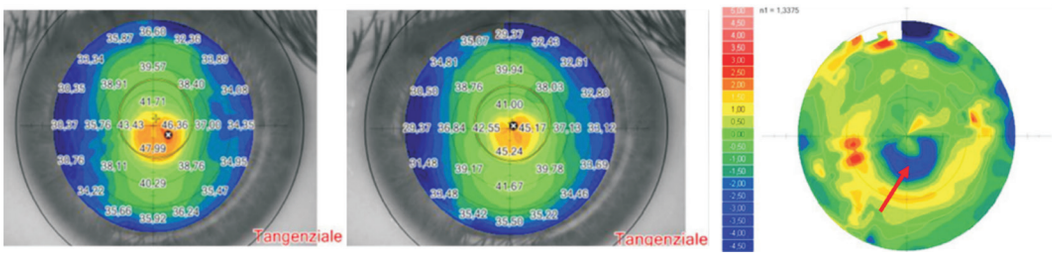

Figure 3 Tomographic differential map (pre- *vs* post-treatment) showing central corneal flattening following 10.0 J/cm² enhanced fluence pulsed light (EFPL) M Epi-On accelerated cross linking (ACXL).

Table 3 Clinical outcomes at baseline and 18mo mean±SD

Parameters	Baseline	18mo	Δ (T0–18mo)	*P*
Kmax, D				
Group 1 (7.2 J/cm²)	48.76±1.92	48.52±2.01	−0.24	0.0029
Group 2 (8.6 J/cm²)	48.40±1.74	48.28±1.68	−0.12	0.0355
Group 3 (10.0 J/cm²)	48.33±1.85	47.30±1.79	−1.03	<0.0001
HOA, μm				
Group 1 (7.2 J/cm²)	0.68±0.14	0.57±0.13	−0.11	0.0023
Group 2 (8.6 J/cm²)	0.69±0.16	0.56±0.15	−0.13	0.0009
Group 3 (10.0 J/cm²)	0.64±0.15	0.34±0.11	−0.30	<0.0001
CDVA, decimal				
Group 1 (7.2 J/cm²)	0.63±0.09	0.77±0.10	+0.14	0.0001
Group 2 (8.6 J/cm²)	0.77±0.11	0.80±0.10	+0.03	0.0706
Group 3 (10.0 J/cm²)	0.75±0.08	0.92±0.07	+0.17	<0.0001

SD: Standard deviation; Kmax: Maximum keratometry; HOA: Higher-order aberrations; CDVA: Best-corrected distance visual acuity.

transepithelial crosslinking efficacy and validate the use of a pachymetry-guided fluence escalation protocol.

In all three treatment arms, riboflavin administration followed the same standardized loading protocol using Paracel I (0.25%) and Paracel II (0.22%), with no variation in concentration or exposure time. UVA irradiation was delivered in pulsed mode for a fixed duration of 13min across all fluence groups (7.2, 8.6, and 10.0 J/cm^2), ensuring uniform conditions aside from fluence modulation.

The observed increase in DL depth with rising fluence is therefore not attributable to enhanced riboflavin diffusion, but rather to the greater photonic energy absorbed within the anterior stroma, resulting in a higher crosslinking density. This is consistent with the improved biomechanical and functional responses noted in the 10.0 J/cm^2 group, which showed the most pronounced corneal flattening, HOAs reduction, and visual recovery. These results suggest that, under conditions of standardized riboflavin loading and irradiation time, fluence is the primary driver of clinical efficacy in PFPL M Epi-On ACXL.

While the percentage depth of the DL relative to corneal thickness (DL/CCT%) was comparable across treatment groups (52.75%–58.04%), the observed differences in clinical and tomographic outcomes suggest that DL depth alone is not a sufficient predictor of efficacy. This observation aligns with previous findings by Mazzotta *et al*[13], who proposed that the DL represents a visible marker of UVA penetration, but its clinical impact depends on the photochemical energy delivered and the resulting density of induced collagen cross-links. Despite comparable DL/CCT% ratios across groups, the markedly superior improvements observed in the 10.0 J/cm^2 group indicate that DL depth alone cannot reliably predict functional outcomes. Instead, the delivered fluence and resulting crosslinking density appear to play a more decisive role in determining treatment efficacy, supporting previous findings that DL should be considered a morphological marker rather than a direct surrogate of biomechanical impact.

In our study, the 10.0 J/cm^2 group demonstrated superior functional gains (*e.g.*, CDVA improvement), corneal flattening (Kmax reduction), and HOA reduction, despite DL/CCT% values being only slightly higher. These findings support the hypothesis that fluence-driven crosslinking density, rather than DL depth alone, plays a central role in the therapeutic response[14-15]. Although no statistically significant differences were found in the percentage depth of the DL among the treatment groups, the clinical and tomographic outcomes varied substantially. This finding is consistent with the concept, previously described by Mazzotta *et al*[13], that the DL should not be interpreted solely as a morphological marker of penetration, but rather as a biophysical surrogate of the cross-linking effect, whose efficacy is primarily governed by the

density of collagen cross-links induced by fluence. Our results reinforce this interpretation, as the 10.0 J/cm^2 group exhibited the most pronounced functional and structural improvements despite comparable DL/CCT ratios.

In transepithelial (Epi-On) CXL, the presence of the epithelium, Bowman's layer, and their associated antioxidant systems leads to a significant absorption of the UVA fluence—approximately 28%–30% of the incident energy is lost before reaching the anterior stroma[16]. Intrinsic shielding effect necessitates an increase in the delivered fluence from 5.4 J/cm^2 to at least 7.2 J/cm^2, to compensate for the optical and biochemical barriers and achieve a comparable biomechanical effect to Epi-Off protocols[1,17]. Assuming a fixed amount of riboflavin in the anterior stroma after imbibition with enhanced formulations, in corneas thinner than 450 μm, a fluence of 7.2 J/cm^2 is sufficient to achieve the necessary percentage of effective CXL relative to the stromal depth. This threshold ensures treatment safety while maintaining efficacy[9]. Conversely, in corneas with a minimum stromal thickness exceeding 450 μm, the use of higher fluence values such as 10 J/cm^2 as showed in this study, results in a greater proportion of the total corneal depth being cross-linked, thereby improving the relative efficiency of the treatment.

The photodynamic effect induced by riboflavin-UVA CXL is known to selectively target aromatic amino acid residues (primarily tyrosine, phenylalanine, and tryptophan), which account for approximately 15% of the total amino acid content in type I collagen. As demonstrated in early biochemical studies by Weadock *et al*[18], the efficiency of crosslink formation is inherently limited by the availability of reactive sites, which introduces the concept of a saturation threshold beyond which additional energy delivery does not translate into further biomechanical benefit unless sufficient volume and spatial exposure are ensured. In this context, fluence becomes the principal modulator of CXL kinetics, allowing clinicians to control the density and extent of covalent bond formation with a fixed riboflavin concentration. This constitutes a monodimensional model of control, effective but incomplete.

Theranostic technologies may evolve this framework by adding a second regulatory dimension, enabling real-time assessment of riboflavin concentration and consumption during treatment. This would support dynamic adjustment of energy delivery based not only on anatomical parameters (*e.g.*, pachymetry) but also on substrate reactivity and biochemical availability, optimizing the coupling efficiency between activated riboflavin and collagen[19-20].

Future theranostic technologies enabling real-time monitoring of riboflavin stromal concentration could allow for dynamic, patient-specific modulation of UVA fluence. This may optimize treatment efficacy beyond what is achievable with fixed pachymetry-based nomograms. One of the key insights of this study is the absence of endothelial cell loss or other adverse effects across all groups. The use of pulsed light delivery (1s on/off), chemically enhanced riboflavin solutions, and strict procedural consistency contributed to this favorable safety profile. These parameters likely improved oxygen kinetics and stromal diffusion[21], critical factors for the success of Epi-On techniques[17].

Notably, the protocol demonstrated full repeatability, suggesting that it may be employed more than once in the same eye without cumulative damage[22]. This opens the door to the use of Epi-On ACXL in early or even preclinical stages of KC, particularly in young adults or patients who may not tolerate Epi-Off techniques[23].

The study also supports the use of the PFPL 10.0 J/cm² protocol as a first-line option in patients over 18y with adequate corneal thickness. For thinner corneas (<420 μm), the 7.2 J/cm^2 protocol remains a viable alternative, albeit with more modest functional outcomes.

The lower age limit of 26y was selected based on the natural history of KC and its impact on treatment response. A recent Meta-analysis of 11 529 untreated eyes[24] demonstrated that younger age strongly predicts faster progression, with an estimated 0.8 D less Kmax steepening per decade and >1.5 D/y progression risk in patients younger than 17y. Similarly, Caporossi *et al*[25] showed that functional improvements and Kmax reductions after CXL are greater in patients <26y, whereas older adults demonstrate reduced corneal plasticity and lower biomechanical responsiveness. Selecting patients ≥26y minimized variability from uncontrolled progression and ensured more homogeneous treatment outcomes in our Epi-On ACXL cohort.

Compared to earlier studies employing fixed-fluence Epi-On CXL, the present work emphasizes the advantages of tailoring fluence to individual pachymetric profiles. This strategic adjustment, combined with a highly standardized and reproducible technique, allows for enhanced clinical results while maintaining the procedural simplicity and safety of the Epi-On approach[1].

A limitation of this study is the absence of an a priori power calculation; however, the sample size is consistent with prospective single-center KC cohorts using strict inclusion criteria and reflects the rarity of progressive cases meeting eligibility requirements. Accordingly, subgroup comparisons should be interpreted as exploratory and hypothesis-generating. More frequent interim analyses were beyond the scope of the predefined study protocol. Further studies with larger cohorts and longer follow-up are warranted to confirm these findings and establish PFPL M Epi-On ACXL as a robust alternative to Epi-Off CXL in standard KC management algorithms.

Recent publications evaluated corneal CXL protocols and have also reported additional outcome monitoring in KC patients undergoing corneal CXL. In contrast, the novelty of the present study lies in a pachymetry-guided progressive-fluence Epi-On protocol (7.2–10.0 J/cm^2) delivered with a fixed irradiation time and standardized riboflavin loading, combined with a prospective 18-month follow-up and subgroup analysis by corneal thickness, highlighting a fluence-dependent effect on functional outcomes, corneal flattening, and HOAs[26-27].

In conclusion, this prospective study confirms that transepithelial (Epi-On) CXL can be effective in halting progressive KC when key procedural parameters are optimized, namely, increased fluence (7.2 to 10.0 J/cm^2), chemically enhanced riboflavin solutions, pulsed UVA delivery, and strict consistency in protocol application. Both 7.2 and 8.6 J/cm^2 fluences demonstrated safety and efficacy in stabilizing disease progression over mid- to long-term follow-up, without adverse effects and with the possibility of repeat treatment. However, 10.0 J/cm^2 fluence yielded the most pronounced benefits in terms of corneal flattening (Kmax), HOA reduction, and functional visual improvement. DL depth was also greater in the 10 J/cm^2 group, confirming deeper biomechanical penetration[28].

Thus, enhanced fluence pulsed light Epi-On ACXL at 10.0 J/cm^2 represents an excellent option for young adults over 18y with baseline pachymetry >400 μm. For thinner corneas, 7.2 J/cm^2 fluence remains a viable alternative. Maintaining consistency in technique execution is crucial to ensure treatment efficacy.

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Conflicts of Interest: Ferrise M, None; **Gagliano C,** None; **D'Esposito F,** None; **Cappellani F,** None; **Zagari M,** None; **Mazzotta C,** None.

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