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Information about the Safety of the Clear-K® Technology

Long-standing basic research into the interaction between laser light and the cornea

Clear-K® treatment uses very low laser power to gently heat the stromal tissue of the cornea beneath the surface of the eye. The temperature profile of this heating has been determined by creating a model of heat flow within the cornea, based on realistic thermal properties of corneal tissue and on the measured surface temperature of the cornea during laser irradiation (Valderrama *et al., SPIE* 1991). A crucial element of the procedure is to hold a sapphire window against the surface of the cornea using gentle vacuum. The sapphire has high thermal conductivity and hence serves as a heat sink, keeping the surface temperature of the cornea low and shifting the peak temperature rise to ~100 µm beneath the surface (Rodgers *et al., SPIE* 2011). The peak temperature is kept below ~80 °C, which avoids any cross-linking or denaturing of collagen (Borja *et al., SPIE* 2004).

Clear-K® has many safety features built in to its design

This design achieves multiple safety features. First, there is no ablation, burning, cutting, or coagulating of tissue – all of which can lead to side effects common in other laser eye treatments and surgeries. Second, the surface cooling prevents a significant temperature rise in Bowman's membrane, a thin layer of tissue ~50 µm beneath the epithelial surface that plays a key role in the wound healing response. Inhibiting the wound healing response is crucial, as this response leads to higher variability in the treatment effect across patients and generally serves to counteract the effects of laser heating. Third, the low laser power also prevents a significant temperature rise in the endothelium, a thin cell layer ~500 µm beneath the surface. The endothelium regulates corneal hydration, having a major impact on the volume of corneal tissue; it is typical for the FDA and other regulatory agencies to require measurements of endothelial cell density as a measure of potential side effects. Clear-K® induces no change in endothelial cell density (OAC Memo, 9 Oct 2017, n=8 patients). Finally, the low laser power and choice of wavelength with high absorption imply that no laser radiation reaches the retina, making it physically impossible to damage or even perturb this sensitive tissue.

Preliminary results from pilot studies show a promising safety record

As a result of these many safety features, Clear-K® currently has an excellent safety record. Our first results in Canada for dry AMD patients report Clear-K® treatment of 32 eyes in 17 patients with no significant adverse events over a follow-up period of 12 months (Stein *et al., F1000 2020*). In our collaboration with three doctors in Canada, a total of 196 eyes in 125 patients have been treated with no significant adverse events. A previous study in Turkey and Croatia treated 10 eyes with Clear-K and observed no significant adverse events after 12 months (Serdarevic *et al., Acta Ophthalmologica* 2017).

<u>Clear-K® incudes significant changes to the shape of the cornea</u>

The mild heating created by Clear-K® induces a change in the material properties of the stromal tissue that has two primary effects: 1) reducing the hydration of the tissue; 2) increasing the modulus. Dehydration of ~40% was measured by Raman spectroscopy, and an increased stiffness of ~50 kPa was measured by atomic force microscopy (Serdarevic *et al*., *Lasers in Surgery and Medicine* 2017). Together, these effects combine to cause a depression in the elevation of the cornea around the treatment spots that peaks at ~15 μm (Stein *et al., F1000 2020*). As a result of this depression, the refraction of the cornea can increase by up to 2.5 diopters (Stein *et al., F1000 2020*). This change in refraction of the cornea redirects light rays away from damages regions of the retina in an AMD patient, thus restoring vision.

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