



John Marshall

# Trials begin on device that remodels the cornea without removal of corneal tissue

Howard Larkin  
in San Francisco

A MICROWAVE device that thermally remodels the cornea by transmitting energy through the epithelium and without removing any corneal tissue has begun trials in Europe to correct myopia on a first cohort of human subjects. Officials at Avedro Inc., Waltham, Massachusetts, US, expect that the

procedure, which is known as Keraflex, will enter US FDA clinical trials later this year.

Avedro executives believe Keraflex may have broader patient appeal than existing refractive procedures because it is completely non-invasive and temporary. It could be commercially available in Europe in 2010.

"We don't see it as competitive to LASIK but as adjunctive to LASIK," said Avedro CEO David Muller PhD, who years ago

headed Summit Technology as it developed the first excimer laser approved by the US FDA. He expects that at least initially Keraflex will be used for patients with myopia of -4.0 dioptres or less.

However, experience with the first group of non-sighted patients treated suggests that -4.0 dioptres may not be the correction limit. "In our initial study we saw patients with corrections up to -10.0 dioptres without induced astigmatism," Dr Muller said. Once the procedure is well understood in low to moderate myopes, patient enrolment criteria may broaden, he added.

## Safety first

Tests so far suggest the procedure is safe, with all of corneas treated regaining complete clarity with no pain within 24 hours. "On the first day post-op, you almost can't tell that anything has been done," Dr Muller said. But while Keraflex technology has been under development for 15 years

at Dartmouth College and has undergone extensive in vitro and in vivo tests, predictability, stability and duration of human corneal remodelling have yet to be precisely determined.

"We have established that the amount of refractive correction is a function of the energy delivered. Our recent limited work has shown that if we increase the energy by 'x' amount, we will increase the correction by 'y' amount. Just as with LASIK, it will take a while to work it out, but the initial results of intended vs. achieved and post-op UCVA have been very promising," Dr Muller said.

Because Keraflex induces changes thermally, it is likely that treatment will regress, as it tends to with other thermal approaches including conductive keratoplasty and earlier laser-based thermal approaches, Dr Muller added. He estimates that Keraflex corrections may have a lifespan of 18 to 24 months. However, it may be possible to extend that range with collagen cross-linking technologies and we will be initiating those trials in the near future, he said.

## Tensioning collagen remodels cornea

Keraflex works by heating collagen fibrils in the stromal layer, altering their chemical structure and causing them to contract. A controlled application of energy close to the surface centrally and peripherally creates tension within the cornea, causing it to flatten and adjust for myopia, said Avedro scientific advisor John Marshall PhD, FMedSci, Rayne Institute, Kings College, St Thomas Hospital, London, UK. Similarly, tensioning stromal fibrils deeper and more peripherally steepens the cornea to correct hyperopia, noted Prof Marshall, who held the excimer laser patent that Summit Technology developed into the LASIK procedure.

The amount of microwave energy delivered by the Avedro device, the Vedula KXS™, can be precisely controlled to achieve the desired pattern and amount of tensioning, Prof Marshall said. Microwave energy propagates between two electrodes held close to the surface of the cornea using a suction ring to maintain positioning. A surface cooling attachment protects the epithelium from thermal damage and helps control how much and how deeply thermal energy is delivered to the stroma. Total treatment time is about two seconds and the equipment required for the procedure is far less complex than for LASIK.

Prof Marshall suggests that a variety of methods might be employed to extend the duration of Keraflex corrections. Once a treatment is completed, ultraviolet radiation could be used to stiffen the corneal collagen much as it does in the natural ageing process. Chemical agents might also be applied to "lock" and "unlock" collagen fibrils to permit adjustments. Avedro intends to develop these concepts, he said.

## Corneal integrity – and market advantage

A major advantage of Keraflex is it does not weaken the cornea, said Prof Marshall. "We are not actually cutting or otherwise damaging the cornea; Keraflex produces a very subtle change." Histological examinations show that collagen fibrils are realigned but not severed with Keraflex as they are when cutting a LASIK flap.

This is important because cutting a flap in LASIK reduces the structural strength of the cornea by 25 to 30 per cent even before any tissue is ablated, Prof Marshall pointed out. Biomechanical research shows that it is the side cut of the LASIK flap that does the most damage, with de-lamination cuts reducing structural strength by only six per cent to 10 per cent.

Prof Marshall allowed that LASIK has been phenomenally successful. Indeed, flap stability issues have been reduced to the point that the procedure is now approved for astronauts, fighter pilots and other active professionals at increased risk of traumatic flap displacement.

Still, the long-term impact of weakening the cornea remains uncertain, Prof Marshall said. "The clinical argument is that flaps are acceptable because we don't see ectasia. But I am not totally interested in ectasia, I am interested in fatigue. Any engineer will tell you that if you decrease intrinsic strength of a structure by 25 to 30 per cent, you will affect its performance over time, especially if it is under dynamic stress. My question is, 20 years down the line, what is the effect of the corneal incision? We really don't know."

Having been intimately involved with the development and commercialisation of PRK and LASIK, both Prof Marshall and Dr Muller believe that Keraflex may have even more market potential.

"Excimer laser surgery started out with PRK, and many in Europe look to PRK first because it does not require cutting a flap. Keraflex is less invasive, so even more people will want to have this procedure," Prof Marshall said.

Dr Muller pointed out that LASIK still has only about two per cent market penetration, and fear of incisions and complications are significant impediments. While the prospect of regression may seem to be a disadvantage, many patients actually see it as a plus, he added. "All the market research we have done indicates that people prefer a temporary procedure, by around four to one, because it is less threatening. We are not reducing the structural integrity of the eye with this procedure, and that is the preferred outcome from both a medical and a consumer perspective."

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