# 1 Efficacy, Safety, Contrast Sensitivity, Aberration Control and 2 year

2 stability after LASIK for high myopia and astigmatism from -8.00 to

# 3 -14.25 D

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## 29 Abstract

30 *Purpose:* To evaluate outcomes of high myopic LASIK using the MEL 80 excimer laser.

31 *Methods:* Retrospective analysis of 479 consecutive high myopic LASIK procedures (318 patients)

32 using the MEL 80 excimer laser (Carl Zeiss Meditec) and VisuMax femtosecond laser (Carl Zeiss

33 Meditec) in 77% of cases or zero compression Hansatome (Bausch & Lomb) microkeratome in 23%

34 of cases. Inclusion criteria were preoperative spherical equivalent refraction (SEQ) of between -8.00

35 D to -14.25 D, and CDVA of 20/20 or better. Patients were followed for a minimum of 1 year. Flap

thickness was between 80-160 μm and optical zone was between 5.75-6.50 mm. Standard outcomes
 analysis was performed.

38 Results: Mean attempted SEQ was -9.39±1.22 D (-8.00 D to -14.18 D) and mean cylinder was -

39 1.03±0.84 D (0.00 D to -4.50 D). Mean age was 37±9 (21 to 60) with 54% female patients. Of this

40 population 69% were treated by DZR and 31% by GIC. Postoperative SEQ was ±0.50 D in 55% and

41 ±1.00 D in 83% of eyes, after primary treatment. After retreatment, 69% of eyes were ±0.50 D and

42 95% were within ±1.00 D. UDVA was 20/20 or better in 89% of eyes after final treatment. One line of

43 CDVA was lost in 3% of eyes and no eyes lost two or more lines. Statistically significant increases

44 (p<0.001) were measured in contrast sensitivity (CSV-1000) at 12 and 18 CPD.

45 *Conclusions:* The MEL 80 excimer laser was found to achieve high efficacy and safety for treatment
46 of high myopia between -8.00 D and -14.25 D and up to -4.50 D of cylinder.

## 48 Introduction

In the 1990s many studies were published reporting PRK and LASIK correction of very high myopia 49 (up to -32.00 D in some cases),<sup>1-6</sup> however, these treatments were associated with low predictability, 50 significant regression, and induced night vision disturbances.<sup>7-9</sup> During this period, it was found that 51 these issues were in large part due to the use of small optical zones,<sup>10, 11</sup> and the non-aspheric 52 Munnerlyn ablation profiles leading to significant induction of spherical aberration.<sup>12</sup> By 1998, authors 53 concluded that LASIK was not an appropriate treatment for very high myopia above -15.00 D<sup>6</sup> and 54 55 were suggesting that phakic intraocular lens (IOL) implantation was more appropriate. Over the next 10 years, consensus shifted towards using phakic IOLs for high myopia and published LASIK studies 56 rarely included myopia above -10.00 D. For example, the German Commission for Refractive 57 Surgery's guidelines state that laser correction should only be considered up to -8.00 D.<sup>13</sup> 58

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This thinking was further reinforced when a Cochrane review was published in 2010<sup>14</sup> (and updated in 60 2014<sup>15</sup>), which compared laser refractive surgery and phakic IOLs for the treatment of high myopia. 61 62 This review concluded that "at one year post surgery, phakic IOLs are safer than excimer laser 63 surgical correction for moderate to high myopia in the range of -6.00 to -20.00 D and phakic IOLs are 64 preferred by patients". However, by applying the rigorous Cochrane method, only three studies met 65 the inclusion condition of being a randomized control trial (RCT), so the conclusion was based on a total of 114 eyes each for LASIK and phakic IOL. Furthermore, the LASIK studies were for first and 66 second generation excimer lasers, two published in 2002 and one in 2007, in which smaller optical 67 zones and/or non-aspheric ablation profiles had been used.<sup>16-18</sup> Therefore, this review had not 68 69 considered modern flying spot excimer lasers, advances in eye-tracking, and ablation profile design including the use of larger optical zones, wavefront-optimized aspheric profiles, <sup>19, 20</sup> modern 70 algorithms for compensation for fluence projection and reflection errors,<sup>21</sup> biomechanical factors<sup>22</sup> and 71 the availability of topography-guided ablation profiles.<sup>23</sup> Advances in femtosecond laser technology 72 also allow ultra-thin flaps,<sup>24</sup> thereby preserving stromal tissue and reducing the risk of ectasia. 73 74

The comparison should also have been considered in the context of safety. The main risks for high
 myopic LASIK are inducing night vision disturbances or keratectasia.<sup>25-28</sup> However, phakic IOLs can
 also cause night vision disturbances,<sup>29</sup> and also introduce less common but potentially serious

78 complications associated with intraocular surgery such as malignant glaucoma, sub-capsular cataract, 79 damage to zonules, macular edema, suprachoroidal hemorrhage, retinal detachment and endophthalmitis.<sup>29-31</sup> Each type of lens also has specific complications that may require intraocular 80 81 surgical intervention (over/undersized lens requiring exchange, explantation, cataract, rotation). Anterior chamber lenses can cause chronic endothelial cell loss<sup>31-33</sup> with an incidence of 0.8% in one 82 study,<sup>33</sup> although another study showed no change in endothelial cell count over 10 years, but 83 concluded this might be related to surgeon expertise.<sup>34</sup> Cataract formation in posterior chamber 84 lenses has been reported to occur in 8.48% of myopic eyes, requiring lens explantation in 3.4% of all 85 eyes.30 86

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The aim of our study was to report outcomes for a large high myopic LASIK population using the MEL 89 80 excimer laser (Carl Zeiss Meditec, Jena, Germany). We also set out to compare other methods for 90 high myopia correction with respect to safety and efficacy.

## 92 Methods

#### 93 Patients

94 This was a retrospective case series of consecutive high myopic LASIK procedures by two 95 experienced surgeons (DZR & GIC) using the MEL 80 excimer laser and VisuMax femtosecond laser 96 (both Carl Zeiss Meditec) or zero compression Hansatome microkeratome (Bausch & Lomb) at the 97 London Vision Clinic, London, UK. Inclusion criteria were attempted spherical equivalent refraction 98 correction of -8.00 D or higher for the primary procedure, medically suitable for LASIK, no signs of 99 keratoconus, no previous ocular, eyelid or orbital surgery, no visually significant cataract, and 100 corrected distance visual acuity (CDVA) 20/20 or better. A minimum follow-up of 1 year was applied. 101 Informed consent and permission to use their data for analysis and publication was obtained from 102 each patient prior to surgery as part of our routine preoperative protocol. 103 104 A full ophthalmologic examination was performed before surgery by an in-house optometrist, as has

been described previously.<sup>19</sup> Manifest refraction was performed using a standardized and validated
protocol.<sup>35</sup> The manifest refraction was repeated on or before the day of surgery by the surgeon,
which was used for treatment planning. Laser data entry was calculated using a multivariate
regression derived nomogram including sphere, spherical aberration precompensation level (see
below), cylinder, age, and flap thickness.

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#### 111 Planning

112 In our protocol for treating high myopia, the predicted residual stromal thickness (RST) must be 113 greater than 250 µm. For some eyes, this meant planning the treatment to be performed in two 114 stages, so that the RST available for further correction could be accurately assessed before planning 115 the second procedure. RST was calculated including safety biases for corneal thickness, flap thickness and ablation depth.<sup>36</sup> The minimum of 10 central handheld ultrasound pachymetry 116 117 measurements was used, less a further 15 µm to allow for the mean overestimation based on our 118 comparison to Artemis very high-frequency digital (VHF) ultrasound (Personal communication, Dan Z Reinstein, 01/09/2006). For flaps created with the zero compression Hansatome using the 160 µm 119 head, we had previously measured our mean central flap thickness to be 119±13 µm.<sup>37</sup> By using a 120 121 160 µm flap thickness in the safety calculation, this incorporated a safety bias of 41 µm, meaning that

122 the achieved central flap thickness would be thicker than 160 µm in only 0.8% of eyes. Similarly, a 123 bias of 18 µm was added to the programmed VisuMax flap thickness, based on our previous study 124 that found the mean central flap thickness to be 2 µm thicker than programmed with a standard 125 deviation of 7.9 µm.<sup>38</sup> Finally, ablation depth was adjusted according to our previous study which 126 found the MEL 80 ablation depth readout overestimated achieved ablation depth by approximately 20%,<sup>39</sup> plus an additional 5 µm bias. Postoperative keratometry was not included as part of the 127 128 suitability assessment; this parameter was formerly used because it acts as a surrogate for induced 129 spherical aberration, but we can now measure the spherical aberration directly.

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Patients in whom full correction could not be achieved using the above RST calculations, a two-stage
protocol was used where the primary procedure was an intentional undercorrection, followed by a
retreatment according to the criteria set out below.

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All patients were given extra consent forms that described the greater risks associated with treating high myopia by LASIK relative to lower corrections, including discussion of night vision disturbances, and refractive accuracy and stability. If a full correction was not possible or the RST indicated that further treatment would be unlikely, another extra consent form was used to clarify that only one treatment might be possible. The alternative of phakic IOL surgery was explained to all patients and that this would enable a full correction. Patients then decided which option to take after weighing up the relative risks and benefits.

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#### 143 Surgical Protocol

All treatments were performed as bilateral simultaneous LASIK. The Hansatome was used between 08/08/2003 and 23/07/2010 in 23% and the VisuMax between 13/04/2007 and 29/12/2011 in 77% of eyes. The procedure was performed by surgeon DZR in 69% and by surgeon GIC in 31% of eyes. The CRS-Master software platform (Carl Zeiss Meditec, Jena, Germany) was used to generate the ablation profiles (version 1.1 until 08/11/2004, version 1.3 until 01/03/2007, version 2.1.6 until 01/11/2009, version 2.3.0 thereafter).

The standardized surgical technique has been described previously.<sup>40, 41</sup> Both the flap and corneal
 ablation were centered on the coaxially sighted corneal light reflex (CSCLR),<sup>42</sup> used as the best
 approximation of the intersection of the visual axis with the cornea.<sup>43</sup>

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The ablation profile used the Tissue Saving Ablation (TSA) profile for the correction of sphere and 155 cylinder, but also included a predetermined level of spherical aberration pre-compensation with a  $Z_4^{0}$ 156 157 value ranging up to 1.21 µm (6 mm zone equivalent). Optical treatment zone diameter for first (TSA) 158 profiles was 5.75 mm in 7%, 6.00 mm in 87%, 6.25 mm in 3%, and 6.50 mm in 3% of eyes. The spherical aberration component was treated at the same diameter as the base ablation in 30% and at 159 160 a 7.00 mm diameter in 70% of eyes. In patients with thinner corneas, the optical zone was reduced to less than 6.00 mm in order to maximize the correction, with the patient counselled for greater risk of 161 162 night vision disturbances. In patients with very large dark pupil diameter, the optical zone was 163 increased if possible according to corneal thickness.

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Intended flap thickness was 160 µm in 23% with the Hansatome, and 80-85 µm in 47%, 90-100 µm in 29%, and 110 µm in 2% of eyes using the VisuMax. Flap diameter ring used was 8.5 mm in 14% and 9.5 mm in 9% of eyes using the Hansatome, while flap diameters with the VisuMax were 8.0 mm in 70%, 8.5 mm in 1%, and 8.8 mm in 5% of eyes. For VisuMax flaps, a small (S) contact glass was used for a 8.0 mm flap diameter otherwise a medium (M) contact glass was used. A 5 mm superior hinge was used in all VisuMax cases.

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Where a full correction was performed, we included an age dependent target hyperopic spherical refraction for all patients younger than 42 years according to a linear function whereby the target sphere was +0.66 D for a 21 year old decreasing to plano for a 42 year old. Our micro-monovision protocol<sup>19</sup> was used for all patients older than 42 years, where the target sphere is plano for the dominant eye and -1.50 D for the non-dominant eye for the majority of patients.

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#### 178 Postoperative Course and Evaluation

Patients were instructed to instill tobramycin & dexamethasone (Tobradex: Alcon, Fort Worth, TX,
USA) and ofloxacin (Exocin: Allergan Ltd, Marlow, UK) four times daily and wear plastic shields for

181 sleeping during the first week. The surgeon reviewed the patient at day one and measured spherical 182 refraction and uncorrected distance visual acuity (UDVA); if necessary, flap adjustments were performed at the slit-lamp using a surgical spear under topical anesthetic and antibiotic cover. An 183 184 optometrist examined the patient at one, three, and twelve months and then yearly thereafter. All 185 visits included measurements of monocular and binocular UDVA, manifest refraction, and corrected 186 distance visual acuity (CDVA). Best-spectacle-corrected mesopic contrast sensitivity was performed 187 at the 3 month visit to compare to baseline. ATLAS corneal topography (Carl Zeiss Meditec, Jena, 188 Germany) and WASCA aberrometry (Carl Zeiss Meditec, Jena, Germany) were performed at 3 189 months, 1 year and 2 years.

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#### 191 **Retreatments**

Retreatments followed the same protocol full correction and two-stage patients. Retreatments were performed once stability was demonstrated after at least 6 months, defined as no change in sphere and cylinder within  $\pm 0.25$  D over an interval of at least two months. A topography-guided ablation<sup>23</sup> was used if the patient reported significant night vision disturbances and it was demonstrated that full spectacle correction alone did not improve night vision disturbances whereas spectacles plus one drop of brimonidine 0.5% did improve night vision disturbances.

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In the majority of cases (66%), where the predicted RST was less than 275 µm, a VHF digital
ultrasound scan was performed to obtain layered pachymetric maps of corneal, epithelial and residual
stromal thickness.<sup>44</sup> The RST map was used to identify the thinnest point and applied in the RST
safety calculation. The retreatment was planned such that the predicted RST after the retreatment
was at least 250 µm at the location of the maximum ablation as well as the location of the minimum
RST. Therefore, in some cases, the retreatment was not necessarily a full correction.

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#### 206 Statistical Analysis

Outcome analysis was performed according to the Standard Graphs for Reporting Refractive
 Surgery.<sup>45</sup> Outcomes were analyzed separately for primary treatment data only, and after the final
 treatment. Data from the 2 year visit were used for analysis if available, otherwise 1 year data was
 used. Stability of keratometry was evaluated by calculating the mean simulated keratometry at 3

- 211 months, 1 year and 2 years. The change in higher order aberrations was assessed by the change in
- coma, spherical aberration and higher order RMS, using a 6 mm analysis zone. Student's t-tests were
- used to calculate the statistical significance of changes in log contrast sensitivity. Microsoft Excel
- 214 2010 (Microsoft Corporation, Seattle, WA, USA) was used for data entry and statistical analysis. A p-
- 215 value <0.05 was defined as statistically significant.

## 216 **Results**

#### 217 **Patient Population**

During the study period, 527 eyes were treated and one year data were available for 479 (91% followup), for which the last timepoint after the primary procedure was 2 years in 48% (n=230), 1 year in 46% (n=221), and 6 months in 6% (n=27) of eyes. All eyes where the last timepoint after the primary procedure was earlier than 1 year had undergone retreatment at that time. For these eyes, 1 year follow-up after the retreatment were used to analyze the final outcome. Table 1 shows the demographic data for the study population.

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#### 225 Retreatments

226 The primary procedure was performed as a partial correction (two-stage protocol) in 16% (79/479) of 227 eyes, of which 71% (56/79) have undergone a retreatment. Of the 400 full correction eyes, 16% 228 (64/400) have undergone a retreatment. Including all eyes, 25% (120/479) of eyes have undergone a 229 retreatment, of which 95% (114/120) were performed as a flap lift, 2.5% (3/120) as a PRK procedure, 230 1.7% (2/120) as a VisuMax LASIK procedure, and 0.8% (1/120) using the VisuMax sidecut only 231 option (to create a flap within the original flap to avoid a zone of epithelial ingrowth scarring). A 232 topography-guided custom ablation profile was used for 8 eyes, which constitutes 1.7% of all 479 eyes treated (6.7% of the 120 retreatments performed), and was used to correct for a decentration in 233 5 eyes, and to enlarge the optical zone in 3 eyes. The scotopic pupil diameter (mean 6.04 mm, range: 234 235 5.34 to 7.10 mm) of this sub-group was not different to that of the population (p=0.282).

#### 237 Standard Outcomes

- Figure 1 shows the outcomes for primary treatments only. Figure 2 shows the final outcomes,
- including retreatments.
- 240

Table 2 shows the normalized contrast sensitivity data preoperatively and after the final treatment. 241 242 There was no change at 3 and 6 cpd, and small but statistically significant increase at 12 and 18 cpd (p<0.001). Table 3 summarizes the ocular aberrations preoperatively and after the primary treatment. 243 244 Coma and higher order RMS were increased, as well as spherical aberration which increased by an 245 average of 0.49 µm. ATLAS keratometry data showed that the mean keratometry was 38.09±1.65 D 246 (range: 32.85 to 42.75 D, n=374) at 3 months, 38.27±1.46 D (range: 34.57 to 42.51 D, n=297) at 1 year, and 38.36±1.47 D (range: 34.06 to 41.98 D, n=168) at 2 years. For 238 eyes with keratometry 247 data at both 3 and 12 months, the mean change was 0.22±0.43 D (range: -1.72 to 1.67 D, p<0.01). 248 249 For 116 eyes with keratometry data at both 1 and 2 years, the mean change was 0.11±0.33 D (range: 250 -0.88 to 1.43 D, p<0.01).

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#### 252 **Complications**

In the 109 eyes with flaps created using the Hansatome there were no intraoperative complications
other than small epithelial defects requiring bandage contact lenses in 3 eyes (2.8%). The appendix
details intraoperative complications for VisuMax flaps and postoperative complications in all eyes.
Overall, across the 31 eyes that had intraoperative and/or postoperative complications, 1 eye lost 1
line of CDVA and none lost more than 1 line.

## 259 **Discussion**

260 The present study found the treatment of myopia between -8.00 D and -14.25 D using the MEL 80 261 excimer laser and either the VisuMax femtosecond laser or zero compression Hansatome microkeratome to be safe and effective. While there was an increase in higher order aberrations, as 262 263 expected for a high myopic correction, this increase was not excessive as demonstrated by no 264 reduction in contrast sensitivity. Safety in terms of change in CDVA was also excellent with no eyes 265 losing 2 lines, 3% losing one line, and 50% gaining one line. While night vision disturbances were not objectively measured, a topography-guided retreatment was available for any patients reporting 266 267 significant symptoms, but was only used in 8 eyes (1.7%) demonstrating that few patients 268 experienced visually significant night vision disturbances.

269

270 In order to compare the current study to published LASIK and phakic IOL studies, we performed a 271 literature review for studies published within the last five years reporting results of myopia above -8.00 D. The main outcome parameters are shown in Table 4,<sup>16-18, 32, 46-50</sup> as well as the studies included in 272 273 the Cochrane review. The results of the present study were similar in terms of accuracy, efficacy and 274 safety to those reported in the last five years for both LASIK and phakic IOLs, although the range treated was much higher for phakic IOLs (e.g. up to -23.00 D<sup>50</sup>). Nevertheless, as discussed earlier, 275 276 intraocular surgery introduces potential, albeit unusual, serious visual complications. While ectasia can occur many years after surgery,<sup>51</sup> with modern keratoconus screening techniques,<sup>52, 53</sup> inclusion 277 278 of biases for calculating predicted RST, direct measurement of RST before retreatment surgery, and the availability of corneal cross-linking,<sup>54</sup> the risk of ectasia is significantly lower than 10 years ago. 279

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It is important to note that the present study and other recent LASIK studies<sup>46-48</sup> appear to contradict 281 the conclusion from the Cochrane review;<sup>14, 15</sup> these results are significantly better than those of both 282 LASIK and phakic IOLs reported for studies included in the Cochrane review. The predictability 283 ranged from 29% to 57% within ±0.50 D for the LASIK/PRK groups and from 24% to 76% for the 284 285 phakic IOL groups in the Cochrane review, whereas the range was from 69% to 100% for recent 286 LASIK studies. Similarly, postoperative UDVA was 20/20 or better in 12% to 84% in the LASIK/PRK 287 groups and 20% to 97% in the phakic IOL groups in the Cochrane review, whereas the range was 288 77% to 92% for recent LASIK studies. Finally, safety was much worse for the LASIK groups in the

Cochrane review with a loss of 2 or more lines of CDVA between 4%<sup>18</sup> and 12% of eyes,<sup>16</sup> whereas 289 290 no eyes lost even 2 lines in the recent LASIK studies. Therefore, it appears that the Cochrane review<sup>14, 15</sup> only included studies that would be considered out-of-date, and the conclusions while 291 292 applicable to earlier technology and protocols do not apply to modern LASIK. This demonstrates the 293 limitation of the Cochrane review methodology to refractive surgery, as very few studies meet the strict criteria of being randomized control trials. This is further emphasized by the fact that the 2014<sup>15</sup> 294 295 update found no new studies meeting the inclusion criteria. While the Cochrane review methodology 296 clearly represents a robust method scientifically, it suffers when applied to refractive surgery as the 297 majority of studies reporting surgical outcomes are retrospective for obvious reasons. This however highlights the paucity of randomized controlled trials, outside of United States Food and Drug 298 Administration trials,<sup>55</sup> as a weakness of the refractive surgery field. 299

300

301 In summary, LASIK for high myopia up to -14.25 D using modern technology was found to have

302 similar outcomes to phakic IOLs, while avoiding the potentially serious complications associated with

intraocular surgery.

## 304 Legends

305 Figure 1: Nine standard graphs for reporting refractive surgery showing the visual and refractive 306 outcomes for 479 high myopic eyes after initial treatment with the MEL 80 excimer laser and the 307 VisuMax femtosecond laser (both Carl Zeiss Meditec) or the zero compression Hansatome 308 microkeratome (Bausch & Lomb). UDVA = uncorrected distance visual acuity; CDVA= corrected 309 distance visual acuity; D = diopters; Postop = postoperative; Preop = preoperative; SEQ = spherical 310 equivalent refraction; TIA = target induced astigmatism; SIA = surgically induced astigmatism. 311 Figure 2: Nine standard graphs for reporting refractive surgery showing the visual and refractive 312 313 outcomes for 479 high myopic eyes after final treatment with the MEL 80 excimer laser and the 314 VisuMax femtosecond laser (both Carl Zeiss Meditec) or the zero compression Hansatome 315 microkeratome (Bausch & Lomb). UDVA = uncorrected distance visual acuity; CDVA= corrected 316 distance visual acuity; D = diopters; Postop = postoperative; Preop = preoperative; SEQ = spherical 317 equivalent refraction; TIA = target induced astigmatism; SIA = surgically induced astigmatism.

### 319 **References**

Knorz MC, Liermann A, Seiberth V, Steiner H, Wiesinger B. Laser in situ keratomileusis to
 correct myopia of -6.00 to -29.00 diopters. J Refract Surg. 1996;12:575-584.

Kim HM, Jung HR. Laser assisted in situ keratomileusis for high myopia. Ophthalmic Surg
 Lasers. 1996;27:S508-511.

324 3. Condon PI, Mulhern M, Fulcher T, Foley-Nolan A, O'Keefe M. Laser intrastromal

keratomileusis for high myopia and myopic astigmatism. Br J Ophthalmol. 1997;81:199-206.

Tsai RJ. Laser in situ keratomileusis for myopia of -2 to -25 diopters. J Refract Surg.
 1997;13:S427-429.

328 5. Marinho A, Pinto MC, Pinto R, Vaz F, Neves MC. LASIK for high myopia: one year

experience. Ophthalmic Surg Lasers. 1996;27:S517-520.

Knorz MC, Wiesinger B, Liermann A, Seiberth V, Liesenhoff H. Laser in situ keratomileusis for
 moderate and high myopia and myopic astigmatism. Ophthalmology. 1998;105:932-940.

Corbett MC, Verma S, O'Brart DP, Oliver KM, Heacock G, Marshall J. Effect of ablation profile
 on wound healing and visual performance 1 year after excimer laser photorefractive keratectomy. Br J
 Ophthalmol. 1996;80:224-234.

335 8. Gartry DS, Kerr Muir MG, Marshall J. Excimer laser photorefractive keratectomy. 18-month
 336 follow-up. Ophthalmology. 1992;99:1209-1219.

Chayet AS, Assil KK, Montes M, Espinosa-Lagana M, Castellanos A, Tsioulias G. Regression
 and its mechanisms after laser in situ keratomileusis in moderate and high myopia. Ophthalmology.
 1998;105:1194-1199.

340 10. O'Brart DP, Corbett MC, Lohmann CP, Kerr Muir MG, Marshall J. The effects of ablation
341 diameter on the outcome of excimer laser photorefractive keratectomy. A prospective, randomized,
342 double-blind study. Arch Ophthalmol. 1995;113:438-443.

343 11. O'Brart DP, Corbett MC, Verma S, Heacock G, Oliver KM, Lohmann CP, Kerr Muir MG,
344 Marshall J. Effects of ablation diameter, depth, and edge contour on the outcome of photorefractive
345 keratectomy. J Refract Surg. 1996;12:50-60.

346 12. Seiler T, Genth U, Holschbach A, Derse M. Aspheric photorefractive keratectomy with
347 excimer laser. Refract Corneal Surg. 1993;9:166-172.

34813.Kohnen T, Strenger A, Klaproth OK. Basic knowledge of refractive surgery: correction of

refractive errors using modern surgical procedures. Dtsch Arztebl Int. 2008;105:163-170; quiz 170162.

Barsam A, Allan BD. Excimer laser refractive surgery versus phakic intraocular lenses for the
 correction of moderate to high myopia. Cochrane Database Syst Rev. 2010:CD007679.

Barsam A, Allan BD. Excimer laser refractive surgery versus phakic intraocular lenses for the
 correction of moderate to high myopia. Cochrane Database Syst Rev. 2014;6:CD007679.

16. El Danasoury MA, El Maghraby A, Gamali TO. Comparison of iris-fixed Artisan lens

implantation with excimer laser in situ keratomileusis in correcting myopia between -9.00 and -19.50

diopters: a randomized study. Ophthalmology. 2002;109:955-964.

358 17. Schallhorn S, Tanzer D, Sanders DR, Sanders ML. Randomized prospective comparison of
visian toric implantable collamer lens and conventional photorefractive keratectomy for moderate to
high myopic astigmatism. J Refract Surg. 2007;23:853-867.

18. Malecaze FJ, Hulin H, Bierer P, Fournie P, Grandjean H, Thalamas C, Guell JL. A

randomized paired eye comparison of two techniques for treating moderately high myopia: LASIK and
 artisan phakic lens. Ophthalmology. 2002;109:1622-1630.

Reinstein DZ, Archer TJ, Gobbe M. LASIK for Myopic Astigmatism and Presbyopia Using
 Non-Linear Aspheric Micro-Monovision with the Carl Zeiss Meditec MEL 80 Platform. J Refract Surg.
 2011;27:23-37.

20. Srivannaboon S, Reinstein DZ, Archer TJ, Chansue E. Spherical Aberration from Myopic

368 Excimer Laser Ablation for Aspheric and Non-Aspheric Profiles. Optom Vis Sci. 2012;89:1211-1218.

369 21. Mrochen M, Seiler T. Influence of corneal curvature on calculation of ablation patterns used in

370 photorefractive laser surgery. J Refract Surg. 2001;17:S584-587.

371 22. Dupps WJ, Jr., Roberts C. Effect of acute biomechanical changes on corneal curvature after
372 photokeratectomy. J Refract Surg. 2001;17:658-669.

373 23. Reinstein DZ, Archer TJ, Gobbe M. Combined corneal topography and corneal wavefront

374 data in the treatment of corneal irregularity and refractive error in LASIK or PRK using the Carl Zeiss

375 Meditec MEL80 and CRS Master. J Refract Surg. 2009;25:503-515.

Lim DH, Keum JE, Ju WK, Lee JH, Chung TY, Chung ES. Prospective contralateral eye study
to compare 80- and 120-mum flap LASIK using the VisuMax femtosecond laser. J Refract Surg.

378 2013;29:462-468.

379 25. Randleman JB. Post-laser in-situ keratomileusis ectasia: current understanding and future
380 directions. Curr Opin Ophthalmol. 2006;17:406-412.

Randleman JB, Caster AI, Banning CS, Stulting RD. Corneal ectasia after photorefractive
 keratectomy. J Cataract Refract Surg. 2006;32:1395-1398.

Randleman JB, Russell B, Ward MA, Thompson KP, Stulting RD. Risk factors and prognosis
for corneal ectasia after LASIK. Ophthalmology. 2003;110:267-275.

385 28. Malecaze F, Coullet J, Calvas P, Fournie P, Arne JL, Brodaty C. Corneal ectasia after

386 photorefractive keratectomy for low myopia. Ophthalmology. 2006;113:742-746.

387 29. Phakic intraocular lenses for the treatment of refractive errors: an evidence-based analysis.

388 Ont Health Technol Assess Ser. 2009;9:1-120.

389 30. Chen LJ, Chang YJ, Kuo JC, Rajagopal R, Azar DT. Metaanalysis of cataract development
after phakic intraocular lens surgery. J Cataract Refract Surg. 2008;34:1181-1200.

391 31. Alio JL, Toffaha BT, Pena-Garcia P, Sadaba LM, Barraquer RI. Phakic intraocular lens

explantation: causes in 240 cases. J Refract Surg. 2015;31:30-35.

393 32. Knorz MC, Lane SS, Holland SP. Angle-supported phakic intraocular lens for correction of
 394 moderate to high myopia: Three-year interim results in international multicenter studies. Journal of

395 Cataract & Refractive Surgery. 2011;37:469-480.

396 33. Guell JL, Morral M, Gris O, Gaytan J, Sisquella M, Manero F. Five-Year Follow-up of 399

Phakic Artisan-Verisyse Implantation for Myopia, Hyperopia, and/or Astigmatism. Ophthalmology.2007.

34. Tahzib NG, Nuijts RM, Wu WY, Budo CJ. Long-term study of Artisan phakic intraocular lens
implantation for the correction of moderate to high myopia: ten-year follow-up results. Ophthalmology.
2007;114:1133-1142.

402 35. Reinstein DZ, Yap TE, Carp GI, Archer TJ, Gobbe M. Reproducibility of manifest refraction
403 between surgeons and optometrists in a clinical refractive surgery practice. J Cataract Refract Surg.
404 2014;40:450-459.

36. Reinstein DZ, Srivannaboon S, Archer TJ, Silverman RH, Sutton H, Coleman DJ. Probability
model of the inaccuracy of residual stromal thickness prediction to reduce the risk of ectasia after
LASIK part I: quantifying individual risk. J Refract Surg. 2006;22:851-860.

37. Reinstein DZ, Archer TJ, Gobbe M. LASIK flap thickness profile and reproducibility of the
standard vs zero compression Hansatome microkeratomes: three-dimensional display with Artemis
VHF digital ultrasound. J Refract Surg. 2011;27:417-426.

- 411 38. Reinstein DZ, Archer TJ, Gobbe M, Johnson N. Accuracy and Reproducibility of Artemis
- 412 Central Flap Thickness and Visual Outcomes of LASIK With the Carl Zeiss Meditec VisuMax
- 413 Femtosecond Laser and MEL 80 Excimer Laser Platforms. J Refract Surg. 2010;26:107-119.

414 39. Reinstein DZ, Archer TJ, Gobbe M. Corneal Ablation Depth Readout of the MEL80 Excimer

415 Laser Compared to Artemis Three-dimensional Very High-frequency Digital Ultrasound Stromal

- 416 Measurements. J Refract Surg. 2010;26:949-959.
- 417 40. Reinstein DZ, Carp GI, de Benedictis D, Archer TJ, Gobbe M, Khan R, von Borch M.
- 418 Standardization of LASIK surgical technique evaluated by comparison of procedure time between two
- 419 experienced surgeons. J Cataract Refract Surg. 2015;41:1004-1008.
- 420 41. Reinstein DZ, Archer TJ. Real-time bilateral LASIK procedure. Available at:
- 421 <u>https://www.youtube.com/watch?v=ncSWnXpgYd0</u>. Accessed 01/12/2014.
- 422 42. Reinstein DZ, Gobbe M, Archer TJ. Coaxially sighted corneal light reflex versus entrance
- 423 pupil center centration of moderate to high hyperopic corneal ablations in eyes with small and large
- 424 angle kappa. J Refract Surg. 2013;29:518-525.
- 425 43. Pande M, Hillman JS. Optical zone centration in keratorefractive surgery. Entrance pupil
- 426 center, visual axis, coaxially sighted corneal reflex, or geometric corneal center? Ophthalmology.
- 427 1993;100:1230-1237.
- 428 44. Reinstein DZ, Archer TJ, Gobbe M. Comparison of residual stromal bed thickness
- 429 measurement among very high-frequency digital ultrasound, intraoperative handheld ultrasound, and
- 430 optical coherence tomography. J Refract Surg. 2012;28:42-47.
- 431 45. Reinstein DZ, Archer TJ, Randleman JB. JRS Standard for Reporting Astigmatism Outcomes
- 432 of Refractive Surgery. J Refract Surg. 2014;30:654-659.

433 46. Kanellopoulos AJMD, Asimellis GP. Refractive and Keratometric Stability in High Myopic

434 LASIK With High-Frequency Femtosecond and Excimer Lasers. Journal of Refractive Surgery.

435 2013;29:832-837.

436 47. Stonecipher KGMD, Kezirian GMMD, Stonecipher M. LASIK for -6.00 to -12.00 D of Myopia

437 with up to 3.00 D of Cylinder Using the ALLEGRETTO WAVE: 3- and 6-Month Results with the 200-

and 400-Hz Platforms. Journal of Refractive Surgery. 2010;26:S814-818.

439 48. Vega-Estrada AMDM, Alió JLMDP, Mosquera SAM, Moreno LJM. Corneal Higher Order

440 Aberrations After LASIK for High Myopia With a Fast Repetition Rate Excimer Laser, Optimized

Ablation Profile, and Femtosecond Laser--assisted Flap. Journal of Refractive Surgery. 2012;28:689-

442 696.

443 49. Hashemi H, Miraftab M, Asgari S. Comparison of the visual outcomes between PRK-MMC
444 and phakic IOL implantation in high myopic patients. Eye. 2014.

445 50. Ju Y, Gao X-W, Ren B. Posterior chamber phakic intraocular lens implantation for high

446 myopia. International journal of ophthalmology, 2013:831-835.

51. Said A, Hamade IH, Tabbara KF. Late onset corneal ectasia after LASIK surgery. Saudi J
Ophthalmol. 2011;25:225-230.

449 52. Ambrosio R, Jr., Caiado AL, Guerra FP, Louzada R, Roy AS, Luz A, Dupps WJ, Belin MW.
450 Novel pachymetric parameters based on corneal tomography for diagnosing keratoconus. J Refract

451 Surg. 2011;27:753-758.

452 53. Silverman RH, Urs R, Roychoudhury A, Archer TJ, Gobbe M, Reinstein DZ. Epithelial

453 remodeling as basis for machine-based identification of keratoconus. Invest Ophthalmol Vis Sci.

454 2014;55:1580-1587.

455 54. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the
456 treatment of keratoconus. Am J Ophthalmol. 2003;135:620-627.

457 55. FDA. WaveLight ALLEGRETTO WAVE™ Excimer Laser System (PMA). Available at:

458 <u>http://www.accessdata.fda.gov/cdrh\_docs/pdf3/P030008b.pdf</u>. Accessed 11/07/2014.

#### Intraoperative complications

	Occurrences	Percentage of Total		
Epithelial Defect	8	2.2%		
Suction Loss	7	1.9%		
Incomplete Flap (Edge)	2	0.5%		
Incomplete Flap (Ablation Zone)	1	0.3%		
Buttonhole	4	1.1%		
Free Cap	0	0%		
Irregular Bed	0	0%		
Flap Tear	1	0.3%		

#### Postoperative complications requiring flap lift

	Occurrences	Percentage of Total			
Flap Lift for Trauma	1	0.3%			
Flap Lift for Epithelial Ingrowth	2	0.5%			
Flap Lift for Microfolds	1	0.3%			
Flap Lift for Interface Deposits	1	0.3%			

### Intraoperative Complications

**Hansatome treated eyes:** There were no intraoperative complications in the 109 eyes treated using the Hansatome microkeratome other than a small epithelial defect requiring a bandage contact lens in 3 eyes (2.8%). There was no impact on CDVA in any of these cases.

**VisuMax treated eyes:** Of the 371 eyes treated using the VisuMax femtosecond laser, a peripheral epithelial defect requiring a bandage contact lens occurred in 8 eyes (2.2%). Suction loss occurred in 7 eyes (1.9%), 5 eyes in which the contact glass was immediately reapplied and flap creation completed with the same flap parameters; of these, a perfect flap was created in 4 eyes with the stromal bed appearing smooth prior to ablation. In the remaining eye some thin thread-like mid-peripheral stromal slivers were noted on the stromal bed with the central bed of good quality for ablation; the peripheral stromal slivers were repositioned before the excimer laser ablation was performed and the flap was repositioned perfectly with no subsequent loss of best spectacle corrected vision or contrast sensitivity. The remaining 2 eyes with repeated suction loss belonged to the same patient, where after four attempts on the first eye and one attempt on the second eye it was deemed

not possible to adequately create flaps using the VisuMax. After discussion with the patient, the procedures were performed instead using the zero compression Hansatome microkeratome without further complication. In all 8 eyes that experienced a suction loss, there was no loss of CDVA nor contrast sensitivity, and 7 eyes actually experienced a gain of one line of CDVA. Further recorded complications in VisuMax treated eyes included one eye (0.3%) with a small tear to the hinge of the flap in an eye that subsequently gained two lines of CDVA; a small peripheral flap tear approximately 1 mm within the flap boundary inferiorly in one eye (0.3%) where the flap lifting instrument perforated the flap while manually dissecting through a peripheral zone of dense opague bubble layer (OBL) due to the presence of a small cryptic buttonhole in an 80 (programmed 98)  $\mu$ m flap – after ablation the flap was repositioned perfectly, a bandage contact lens was applied and after healing there was no change in CDVA. There were 3 eyes (0.8%) in which there was inadequate or no femtosecond cutting within a small area of flap interface (centrally in 1 eye, peripherally in 2 eyes); in each case these areas could be dissected manually and there was no impact on CDVA or contrast sensitivity. Finally, there were 4 eyes (1.1%) in which a small buttonhole was discovered on lifting the flap (centrally in 1 eye, peripherally in 3 eyes) probably secondary to previous focal contact lens related infections (with epithelial plugs). In all cases, after carefully lifting the flap, the residual epithelium overlying Bowman's layer was brushed off to reveal the stromal surface and the ablation was performed and flap replaced carefully followed by an overnight bandage contact lens. The eye with a central buttonhole lost one line of CDVA.

#### Postoperative complications requiring flap lift

A flap lift procedure was required at the 1 day visit to reposition the flap in 1 eye (0.3%) following a flap slip due to trauma to the eye overnight. This eye then also required a second flap lift procedure 1 week later for epithelial ingrowth removal which healed with no ingrowth. One other eye (0.3%) required a flap lift procedure for epithelial ingrowth following a retreatment procedure. A flap lift procedure was performed for 1 eye (0.3%) to treat microfolds at the 1 month timepoint. A flap lift procedure was performed for 1 eye (0.3%) to remove inorganic deposits from the flap interface. There was no impact on CDVA in any of these cases.

# Table 1: Study demographics

Number of Eyes (patients)	479 (318)
Age (years)	37±9 (21 to 60)
Gender Ratio (M/F %)	46 / 54
Attempted Spherical Equivalent Refraction (D)	-9.39±1.22 (-8.00 to -14.18)
Attempted Cylinder (D)	-1.03±0.84 (0.00 to -4.50)
Scotopic pupil (mm)	5.80±1.04 (3.36 to 8.40)

# Table 2: Normalized mesopic contrast sensitivity (CSV-1000)

	3 CPD	6 CPD	12 CPD	18 CPD
Pre	0.99±0.11	0.94±0.09	0.91±0.13	0.84±0.19
Post	0.98±0.11	0.94±0.09	0.93±0.13	0.87±0.20
p-value	0.127	0.249	<0.001	<0.001

CPD: Cycles Per Degree

# Table 3: Ocular Aberrations (µm)

	Pre	Post	Change	t-test
Coma	0.169±0.103	0.266±0.201	0.100±0.221	p<0.001
Spherical Aberration	0.135±0.148	0.626±0.222	0.491±0.074	p<0.001
HORMS	0.324±0.109	0.737±0.198	0.426±0.196	p<0.001

HORMS: High Order Root Mean Square

		1				Accuracy		UDVA			Safety		
First Author	N (eyes)	Technique	Preop SEQ (D)	Age (years)	FU	Mean±SD (D) (range)	±0.50	±1.00	Pre CDVA ≤20/20	≤20/20	≤20/40	1 line	≥2 lines
Reinstein 2014	483	LASIK VisuMax/Hansatome CZM MEL80	-9.57±1.29 (-7.50 to -14.18)	36.8±9.4 (21 to 60)	1-2 years	-0.26±0.47 (-2.25 to +1.13)	69%	95%	100%	89%	99%	3%	0%
Kanellopoulos 2013	116	LASIK Wavelight FS200 Wavelight EX500	-7.67±1.55 (-6.00 to -13.00)	28.7 ± 7.5 (17 to 51)	3 months	-0.37±0.08	89%	95%	73%	90.5%	97.4%	1.7%	0%
Vega-Estrada 2012	29	LASIK IntraLase Schwind AMARIS	-8.39±0.93 (-6.75 to -11.25)	36.7 ±10.8 (24 to 61)	6 months	-0.42±0.82 (-3.50 to +0.63)	-	89.6%	-	-	-	-	-
Stonecipher 2010	65	LASIK IntraLase Alcon Allegretto Wave 400Hz	-7.07±0.89 (-6.86 to -12.63)	33.8 (20 to 60)	6 months	-	100%	100%	-	92%	100%	-	0%
Stonecipher 2010	141	LASIK IntraLase Alcon Allegretto Wave 200Hz	-6.76±1.01 (-6.08 to -11.05)	33.8 (20 to 60)	6 months	-	86%	100%	-	77%	100%	-	0%
Hashemi 2014	23	PRK-MMC VISX STAR S4	-8.82±1.25 (≤ -8.00)	28.7±5.3	1 year	-0.25±0.41	85.7%	-	76.2%	57.1%	-	9.5%	0%
Hashemi 2014	23	Phakic IOL Artiflex	-9.49±1.94 (≤ -8.00)	27.7±5.3	1 year	-0.17±1.17	95.7%	-	95.7%	73.9%	-	0%	0%
Ju 2013	82	Phakic IOL STAAR ICL	-15.56±4.35 (-9.00 to -23.00)	28.6 ± 7.6 (19 to 45)	3 months	-1.85±0.72	72.5%	88%	45%	58.5%	92.7%	3.7%	-
Knorz 2011	104	Phakic IOL AcrySof Cachet	-10.41±2.31 (-6.00 to -16.50)	36.6 ± 8.1 (18 to 53)	3 years	-0.24±0.55 (-2.00 to +1.63)	78.8%	91.3%	100%	71.2%	98.1%	1%	1%
Alió 2014	40	LASIK VISX 20/20	(-6.00 to -18.00)	51.1±6.7 (35 to 60)	15 years	-1.37±2.21	-	46.2%	-	43.6%	64.1%	10.3%	0%
Oruçoğlu 2012	143 39 FU	LASIK Technolas	-21.70±5.80 (-38.00 to -14.13)	-	10 years	-6.09±3.35 (-14.38 to -0.50)	-	14% 1 year	-	-	2.6%	10.3%	-
El Danasoury 2002	45	LASIK NIDEK EC-5000	-13.24±2.30 (-9.13 to -17.50)	33.7±7.1 (21 to 47)	1 year	-0.87±0.8 (-3.00 to -1.00)	29%	56%	-	12.2%	58.5%	-	12.2%
El Danasoury 2002	45	Phakic IOL Artisan	-13.93±2.90 (-9.50 to -19.38)	33.7±7.1 (21 to 47)	1 year	-0.64±0.8	42%	65%	-	20.9%	88.4%	-	0%
Malecaze 2002	25	LASIK Hansatome Technolas	-9.39±1.47 (-8.00 to -12.00)	38.4±7.6 (31 to 52)	1 year	-0.74±0.67	44%	64%	-	24%	80%	20%	4%

Malecaze 2002	25	Phakic IOL Artisan	-10.19±1.56 (-8.00 to -12.00)	38.4±7.6 (31 to 52)	1 year	-0.95±0.45	24%	60%	-	20%	60%	12%	0%
Schallhorn 2007	45	PRK VISX S3	-8.30±1.25	32.6±7.0	1 year	+0.60±0.75	57%	80%	89%	82%	-	7%	0%
Schallhorn 2007	43	Phakic IOL TICL	-8.04±1.28	30.8±6.0	1 year	+0.27±0.36	76%	100%	93%	97%	-	0%	0%











