ARTICLE

# Pupil dilation dynamics with an intracameral fixed combination of mydriatics and anesthetic during cataract surgery

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**Purpose:** To compare the pupil dynamics of an intracameral combination of 2 mydriatics and 1 anesthetic (Mydrane) to a standard topical regimen for cataract surgery.

**Setting:** Sixty-two centers in Europe and 6 centers in Algeria.

**Design:** Prospective case series.

**Methods:** Pupil size measurements were performed in 2 randomized studies (phase 2 and phase 3) under masked conditions (recorded videography, masked reading center). The outcomes in the phase 2 study supported evaluation of the timeframe to obtain pupil dilation and the phase 3 study provided results on mydriasis stability.

**Results:** Phase 2 and phase 3 comprised 139 patients and 591 patients, respectively. After intracameral combination administration, 95% of the pupil dilation was achieved within a mean of 28.6 seconds ± 4.6 (SD). At the beginning of capsulorhexis creation, the mean pupil diameter was larger than 7.0 mm in both groups. The intraoperative pupil diameter remained stable in the intracameral combination group and decreased in the topical group. The mean change in pupil size just before capsulorhexis to the end of surgery (just before cefuroxime injection) was −0.22 ± 0.72 mm and −1.67 ± 0.98 mm, respectively. No clinically significant change in pupil diameter (change <1.0 mm) occurred in the majority of the intracameral combination group (89.3%) compared with the topical group (26.8%).

**Conclusions:** Intracameral combination of 2 mydriatics and 1 anesthetic is an alternative to topical mydriatics for cataract surgery. The prompt onset of pupil dilation and the stable mydriasis induced by this drug combination improved the intraoperative conditions during crucial steps, such as intraocular lens implantation.

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Cataract surgery with intraocular lens (IOL) implantation requires adequate pupil dilation and stable mydriasis. In a recently published survey,[1] stable mydriasis was rated as the most important factor. Rapid onset of mydriasis was also considered a key factor in this survey. Despite the numerous advances in cataract surgery, mydriasis remains a foremost concern among cataract surgeons.

An adequate pupil diameter facilitates surgical maneuvers and stable mydriasis mitigates intraoperative complications. Despite adequate preoperative dilation, the pupil can constrict unpredictably during surgery as a result of inadvertent instrument contact with the iris, prolonged surgery, surgical microscope illumination, and patient movement. Intraoperative miosis during cataract surgery can jeopardize the quality of IOL implantation,[2,3] which can cause complications including iris trauma and posterior capsule rupture with or without vitreous loss.[4] Intraoperative complications prolong surgery, increasing the risk for endophthalmitis and macular edema from iris trauma and increased surgical manipulation.[2]

Inconsistent mydriasis and pupil constriction are considered significant drawbacks of current topical eyedrop

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regimens for cataract surgery.[3,5] The routine topical eyedrop regimen for cataract surgery includes the repeated instillation of anticholinergic and sympathomimetic agents. The drawbacks of topical application include the delayed onset of mydriasis, limited bioavailability, and non-negligible systemic absorption.[3,6–9] Moreover, multiple doses of eyedrops such as tropicamide, phenylephrine, and topical anesthetics (eg, oxybuprocaine or tetracaine) can result in damage to the ocular surface and, possibly, superficial keratopathy.[A–C] The induced toxic keratopathy might interfere with visualization during surgical procedures.

An alternative to topical mydriatics is an intracameral injection of mydriatics at the beginning of cataract surgery. Compared with topical mydriatics, the benefits of intracameral injection include a faster onset and greater stability of mydriasis.[3] In addition, intracameral mydriasis is a safe and effective alternative to topical mydriasis, with less risk for systemic exposure.[5] Previous studies[3,10] report the safety and efficacy of intracameral mydriatics custom-blended on site. These studies found prompt and stable mydriasis. Recently, an intracameral combination of 2 mydriatics and 1 anesthetic (lidocaine, phenylephrine, and tropicamide) was approved in Europe for cataract surgery to obtain intraoperative mydriasis and intraocular anesthesia.[11] The approved combination drug is produced according to Good Manufacturing Practice standards to ensure safety. It is used in patients who had satisfactory pupil dilation with topical mydriatic therapy at a preoperative assessment. The combination drug is the first standardized ready-to-use ophthalmic combination of tropicamide 0.02%, phenylephrine 0.31%, and lidocaine 1.0%, and the recommended dose is a single injection of 0.2 mL.

During early development of the combination drug, a phase 2 clinical trial supported evaluation of the timeframe to obtaining pupil dilation with the combination drug; the trial followed a methodology comparable to that of Lundberg and Behndig.[3] Further results from a phase 3 study supported assessment of mydriasis stability in a large population (N = 555) during cataract surgery. The methodology and the main efficacy and safety results of the latter study were recently published.[11]

The current study presents results from the phase 2 study of the onset of mydriasis and additional results of the phase 3 study of the stability of mydriasis.

## PATIENTS AND METHODS

The phase 2 and phase 3 clinical studies on the combination drug (Mydrane) were registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database under EudraCT No. 2008-003279-28[D] and 2010-021188-34,[E] respectively, and were performed in Europe for approval purposes. Data issued from these studies were used to compare the timeframe in obtaining pupil dilation, the pupil diameter, and stability of mydriasis (collectively termed pupil dynamics) throughout cataract surgery in patients who received the combination drug at the commencement of surgery (just after corneal incision) (combination drug group) with those in patients who received standard topical mydriatics (topical group) in an ambulatory care setting. The standard topical regimen consisted of 3 instillations of tropicamide 0.5% (Mydriaticum 0.5%) plus 3 instillations of phenylephrine hydrochloride 10.0% (Neo-Synephrine 10.0%) starting 30 minutes before surgery (Table 1). These studies were performed in accordance with the Good Clinical Practice guidelines, the tenets of the Declaration of Helsinki, and the local health regulations. Ethics

**Table 1. Specifications of the phase 2 and phase 3 European Union approval studies of the combination drug for intracameral injection just before cataract surgery began.**

| Parameter | Phase 2 | Phase 3 |
|---|---|---|
| Study type | Pilot, dose-finding study | Pivotal, efficacy, and safety study |
| General design | Prospective, randomized, open-label, parallel-group study<br>Multiple surgeons in 4 countries.<br>Masked assessment of the primary variable by trained operators. | Prospective, randomized, open-label, parallel-group study.<br>Multiple surgeons in 9 countries.<br>Masked assessment of the primary variable by trained operators. |
| Inclusion criteria (selection visit) | Age 18 to 85 years<br>Scheduled to have phacoemulsification with foldable IOL and self-sealing CCIs<br>ECC >2000 cell/mm$^2$<br>Pupil diameter ≥7.0 mm with topical mydriatics* | Age 40 to 88 years<br>Scheduled to have phacoemulsification with foldable IOL and self-sealing CCIs<br>Pupil diameter ≥7.0 mm with topical mydriatics† |
| Study arms | 4 arms:<br>Group 1 received 150 µL ICMA‡<br>Group 2 received 200 µL ICMA‡ (recommended dose)<br>Group 3 received topical mydriatics (tropicamide 0.5% and phenylephrine 10%§)<br>Group 4 received topical mydriatics (tropicamide 0.5% and phenylephrine 10%§) and intracameral lidocaine 1% | 2 arms:<br>ICMA group received 200 µL ICMA‡ (recommended dose)<br>Topical group received topical mydriatics (tropicamide 0.5% and phenylephrine 10%§) |
| Patients (n)¶ | 34 in the ICMA group (Group 2)<br>35 in the topical group (Group 3) | 268 in the ICMA group<br>281 in the topical group |

CCIs = clear corneal incisions; ICMA = intracameral combination of 2 mydriatics and 1 anesthetic
*Measurement of pupil diameter at slitlamp examination after instillation of 1 to 2 drops tropicamide 0.5% and 1 to 2 drops of phenylephrine 10.0%
†The following dilation protocol was used: 1 drop of tropicamide 0.5% + 1 drop of phenylephrine 10.0%, with a maximum of 3 combined instillations at 10-minute intervals
‡One intracameral injection of combined drug; a supplementary injection of 100 µL was permitted at the surgeon's discretion
§One drop each repeated 3 times at 10-minute intervals beginning 30 minutes before surgery
¶This paper presents data for Groups 2 and 3 from phase 2 study only

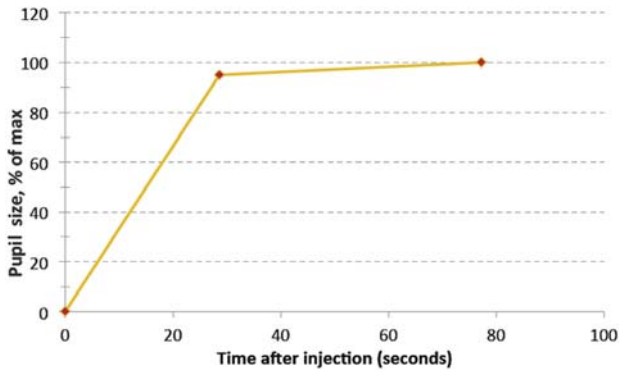


**Figure 1.** Time to maximum pupil dilation after injection of the combination drug in the anterior chamber (phase 2, modified intention-to-treat set) based on 28 patients in Group 2 because 2 patients in this group had no video recording of the surgery.

committee approvals were obtained in each country before and patient was enrolled. Written informed consent was obtained from each patient.

### Study Design and Patient Inclusion Criteria

Table 1 shows the design of both studies. Phase 2 was a pilot study comparing patients having cataract surgery who received 2 doses of the combination drug. Phase 3 was a large-scale confirmatory multicenter international study that used only the approved dose of the combination drug (200 µL). The 2 studies had similar inclusion criteria. The selection visit included the procedures usually performed for the preoperative checkup run for cataract surgery. The pupil diameter had to be at least 7.0 mm within 30 minutes after the standard mydriatic dosing regimen was administered. Contrary to phase 2, the phase 3 study protocol dictated a waiting time of 1.5 minutes (with the surgical microscope light off) after injection of the combination drug and before delivery of an ophthalmic viscosurgical device (OVD), artificially increasing the time between the combination drug administration and the OVD injection. Most assessments and procedures, including pupil size measurements, were standardized. Measurement of the pupil size parameters was performed under standardized masked conditions, as described below.

### Pupil Dynamics Parameters

In both studies, all cataract surgeries were video recorded. The pupil diameter throughout surgery was measured in phase 2 and phase 3 using the methodology described by Labetoulle et al.[11] Measurements were centralized and performed by independent masked trained operators based on photographs at 5 times during surgery as follows: just before the corneal incision (T1), just before injection of the OVD (T2), just before the capsulorhexis (T3), just before IOL insertion (T4), and just before cefuroxime injection (end of surgery) (T5). Any other medications used to obtain and maintain mydriasis preoperatively or intraoperatively were noted. The pupil size just before OVD injection was defined as the maximum mydriasis.

In phase 2, the measurements allowed calculation of the time to maximum mydriasis without a mandatory waiting time. Then, the time to achieve 95% maximum mydriasis was assessed for the combination drug. In addition, the time to achieve sufficient mydriasis was also evaluated based on the surgeon's estimation. In the phase 3 study, the maximum change in pupil size during surgery (from just before capsulorhexis to the end of surgery) was calculated. In addition, the effect of a second injection of the combination drug in stimulating any additional mydriasis was evaluated.

### Statistical Analysis

Data were analyzed in the modified intention-to-treat set; that is, all patients for whom there was evidence that they received the study medications and who satisfied the exclusion criteria concerning unauthorized previous and concomitant medications likely to influence mydriasis. Number of patients was set according Labetoulle et al.[11] Descriptive statistics are reported here.

## RESULTS

In phase 2, the modified intention-to-treat set comprised 30 patients in the combination drug group and 32 patients in the topical group. In phase 3, the modified intention-to-treat set comprised 549 patients (268 in combination drug group, 281 in topical group).

### Time to Obtain Pupil Dilation

In phase 2, the mean time estimated by the surgeons to achieve mydriasis was 20 minutes $\pm$ 7 (SD) in the topical group and 35 $\pm$ 27 seconds in the combination drug group. Based on pupil size measurements in the combination drug group, 95% of the pupil dilation was achieved by a mean of 28.6 $\pm$ 4.6 seconds after intracameral administration of the combination drug (Figure 1).

### Stability of Mydriasis

Table 2 shows the pupil dilation during various stages of surgery in both studies. From before initiation of the capsulorhexis to the end of surgery, the mean pupil diameter was larger than 7.0 mm in both groups, with a slightly larger mean pupil size in the reference group. The mean pupil diameter remained stable during surgery in the combination drug group and decreased in the topical group.

The number of cases with at least a 6.0 mm pupil diameter (commonly considered adequate to perform surgery from capsulorhexis forward under good conditions) during the surgery ranged from 244 (97.6%) of 250 patients (before capsulorhexis) and 216 (92.7%) of 233 patients (just before cefuroxime injection/end of surgery) in the intracameral combination group and all 286 patients (100%) (before capsulorhexis) and 201 (81.7%) of 246 patients (end of surgery) in the topical group (Figure 2). In both phase 2 and phase 3, no patient in the intracameral combination group had a pupil smaller than 5.0 mm before IOL implantation; 1 (0.4%) of 233 patients in the phase 3 study had a pupil smaller pupil than 5.0 mm at the end of surgery (Figure 2). In contrast, in the topical group, 3 (1.2%) of 259 patients before IOL implantation and 2 (7.7%) of 26 patients at the end of surgery had a pupil diameter smaller than 5.0 mm.

The mean change in pupil size just before capsulorhexis to the end of surgery was $-0.22 \pm 0.72$ mm (range $-3.90$ to 1.80 mm; median $-0.10$ mm) in the intracameral combination group and $-1.67 \pm 0.98$ mm (range $-5.60$ to 0.10 mm; median $-1.51$ mm) in the topical group. Table 3 shows the stratification of intraoperative change in pupil diameters from just before capsulorhexis to the end of surgery. No clinically significant change in pupil diameter (change $<1$ mm) was noted in the majority of intracameral combination patients (208 patients [89.3%]) compared with the topical group (65 patients [26.8%]). A significant

**Table 2. Mean pupil size during various stages of cataract surgery in the combined group and topical group (modified intention-to-treat set).**

| Stage | Mean Pupil Size (mm) ± SD | | | |
|---|---|---|---|---|
| | Phase 2 | | Phase 3 | |
| | Combined Group* (n = 30) | Topical Group (n = 32) | Combined Group* (n = 268) | Topical Group (n = 281) |
| Before capsulorhexis | 7.4 ± 0.8 | 8.7 ± 0.9 | 7.7 ± 0.9 | 8.9 ± 0.9 |
| Before IOL insertion | 7.6 ± 0.9 | 7.6 ± 1.2 | 7.7 ± 0.9 | 7.8 ± 1.1 |
| End of surgery | 7.7 ± 1.0 | 7. 5 ± 1.4 | 7.5 ± 1.0 | 7.2 ± 1.3 |

IOL = intraocular lens
*Five patients and 71 patients received more than one combined drug injection in phase 2 and phase 3, respectively

decrease in pupil size (≥3 mm) during surgery occurred in 1 patient (0.4%) in the intracameral combination group and in 20 patients (8.2%) in the topical group.

### Effect of Second Injection on Pupil Dilation

In phase 2, 5 patients (16.7%) (in Group 2 only) in the modified intention-to-treat set received a supplementary injection of the combination drug. In phase 3, 71 patients (26.5%) received more than 1 injection of the combination drug at the discretion of the investigator. Based on the modified intention-to-treat set in the phase 3 study, the mean increase in pupil diameter after the second administration of the combination drug was 0.20 ± 0.50 mm (range −1.7 to 1.6 mm; median 0.15 mm), suggesting no clinically significant added value of an additional injection of the combination drug.

## DISCUSSION

The results in the phase 2 and phase 3 studies indicate that the combination drug (Mydrane) triggered prompt onset of pupil dilation and stable mydriasis suitable for performing routine cataract surgery, including the step of checking the correct alignment of toric IOLs. The intracameral combination drug provided pupil dynamics that are consistent with the Swedish experience using intracameral mydriatics custom-blended in-house.[3,5] We found that pupil size with the combination drug increased rapidly after a single intracameral injection (maximum mydriatic effect achieved in <30 seconds) and then continued to increase (slightly) before stabilizing during surgery.

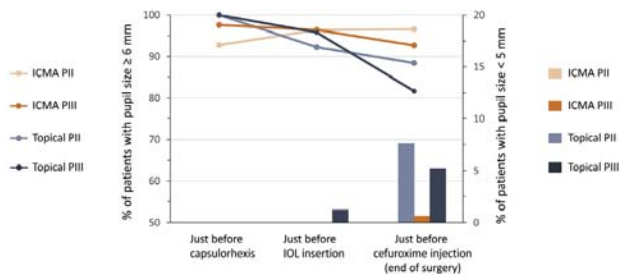


**Figure 2.** Percentage of patients with a pupil diameter of 6.0 mm or larger (*lines*) and percentage of patients with a pupil diameter smaller than 5.0 mm (*bars*) at various stages of cataract surgery in patients who received the combination drug or a standard topical regimen of mydriatics (ICMA = intracameral combination of 2 mydriatics and 1 anesthetic; IOL = intraocular lens; PII = phase 2; PIII = phase 3).

The pupil dynamics of the combination drug are the result of the constituents of this fixed combination of 2 mydriatics and 1 anesthetic as well as the intracameral delivery. The prompt onset of pupil dilation in this study is likely the result of the effect of the mydriatics being delivered almost directly to the site of action (iris). The slow penetration of topically applied drugs in the anterior chamber was evident by the time it took to observe the pharmacodynamic effects, with the cornea considered the main route of penetration and the main barrier. In addition, it is estimated that less than 1%, and, possibly up to 10%, of the topical dose enters the anterior chamber while more than 50% is absorbed into systemic circulation.[12–14] Finally, the lack of an additional effect of a second injection could be explained by the pharmacodynamics (competitive binding for iris receptors) of the mydriatic agents in the combination drug.

The time to achieve adequate mydriasis was much longer with the topical regimen than with the combination drug (at least 20 minutes versus fewer than 30 seconds). Lundberg and Behndig's[3] comparison of topical mydriatics and custom-blended intracameral mydriatics also found a

**Table 3. Stratification of intraoperative change in pupil diameter starting just before capsulorhexis to the end of surgery by group (phase 3; modified intention-to-treat set).**

| Change | Number (%) | |
|---|---|---|
| | Combined Group (n = 233) | Topical Group (n = 243) |
| Increase or decrease <0.5 mm | 171 (73.4) | 17 (7.0) |
| Decrease ≥0.5 mm to <1.0 mm | 37 (15.9) | 48 (19.8) |
| Decrease ≥1.0 mm to <2.0 mm | 18 (7.7) | 99 (40.7) |
| Decrease ≥2.0 mm to <3.0 mm | 6 (2.6)* | 59 (24.3) |
| Decrease ≥3.0 | 1 (0.4) | 20 (8.2)† |

*One patient in the combined group received acetylcholine at the end of surgery (between IOL implantation and the end of surgery) to reduce mydriasis
†One patient in the topical group received miotics (acetylcholine chloride [Miochol-E]) at the end of surgery (between IOL implantation and the end of surgery) to reduce excessive pupil dilation

much faster onset of mydriasis with the intracameral protocol for cataract surgery. The prompt onset of pupil dilation induced by the combination drug directly in the operating room allows the surgeon to induce mydriasis when it is required.

In addition to providing prompt onset of mydriasis, the administration of the combination drug ensures a pupil that is sufficiently enlarged for good surgical conditions. At present, a planned capsulotomy diameter of 5.5 mm requires a pupil size at least of 6.0 mm to account for a 0.5 mm circumferential safety zone.[15] In both studies (phase 2 and phase 3), both groups had a mean pupil diameter of at least 7.0 mm from before initiation of the capsulorhexis to the end of surgery, which is more than adequate for phacoemulsification with IOL implantation.

The mydriasis obtained with the combination drug was stable. The mean decrease in pupil diameter (−0.22 mm) in the interval just before capsulorhexis creation to the end of surgery was not clinically significant in the combination drug group, and it was higher in the topical group (−1.67 mm). Moreover, a significant decrease in pupil size (≥3.0 mm) during surgery occurred in 8.2% of patients in the topical group, which could have significantly affected the outcomes of surgery. Taken together, these findings indicate that the stability of mydriasis was greater with the combination drug than with the topical regimen. Our observations of stability concur with those of Lundberg and Behndig,[3] who found statistically significantly greater pupil miosis in the topical group than in an intracameral mydriatic group. The mydriatic effect of the intracameral lidocaine might also be a reason of the greater stability of mydriasis with the combination drug. Lidocaine at high concentrations impedes membrane depolarization of the motor neurons innervating the muscles of the iris stroma. Because discomfort or pain induces miosis, the anesthetic effect of lidocaine (ie, paralysis of iris muscles, especially the iris sphincter) might contribute to the increased stability of pupil dilation.[16,17] Outcomes from phase 3 indicate that patients in the combination drug group had statistically significantly less pain or sensation of pressure than patients in the topical group just before IOL insertion ($P = .034$).[11]

Stability of mydriasis during surgery is imperative for mitigating intraoperative complications. A stable pupil during surgery with the combination drug might facilitate some critical maneuvers, such as cortical cleaning, capsule polishing, and IOL implantation. This is particularly significant for the insertion of toric IOLs, for which good iris dilation is mandatory at the final step of surgery. In the 2013 European Observatory of Cataract Surgery survey,[1] the importance of stable mydriasis during surgery was rated as 9.0 on a 10-point scale. The overall results of this survey also indicate that stable mydriasis was more important to surgeons than the "largest size of dilation." Initially, pupils might be larger with topical mydriatics; however, intraoperative pupil miosis is more pronounced or unpredictable compared with that achieved with intracameral mydriatics.[5] Pupil miosis during surgery might be associated with more challenging cases and a host of vision-threatening complications, such as posterior capsule rupture and vitreous loss.[4] In this regard, the phase 3 data analysis showed a statistically significant lower rate of technically challenging cases during IOL implantation in the combination drug group than in the topical group as graded by the surgeons ($P = .047$).[11] We also noted a lower number of posterior capsule ruptures in the combination drug group (1 case [0.4% of patients]) than in the topical group (4 cases [1.4%]) in phase 3.[11] The 1 case of posterior capsule rupture in the combination group should not have been included in the study because of the presence of traumatic cataract and zonular weakness preoperatively.

In summary, in these studies of a relatively large number of patients, the combination drug induced prompt onset and stable mydriasis with a large pupil diameter throughout cataract surgery. The combination drug provided maximum dilation with a single dose, and additional dilation was not achieved with additional doses. Thus, the combination drug can be considered an alternative to mydriatic eyedrops for cataract surgery, yielding a significant improvement in pupil dynamics. The pupil dynamics induced by the combination drug enhanced the intraoperative conditions during crucial maneuvers, such as capsulorhexis, IOL implantation, and accurate positioning of toric IOLs.

### WHAT WAS KNOWN

- Before cataract surgery, the surgical eye commonly has repeated instillation of anticholinergic and sympathomimetic agents. However, there are drawbacks to this topical regimen, including intraoperative miosis and a delay in achieving adequate mydriasis.

### WHAT THIS PAPER ADDS

- The combination drug induced prompt and stable mydriasis and can serve as an alternative to the topical regimen, resulting in a significant improvement in pupil dynamics for performing cataract surgery.

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