One-Year, Randomized Study Comparing Bimatoprost and Timolol in Glaucoma and Ocular Hypertension

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**Objective:** To compare bimatoprost with timolol maleate in patients with glaucoma or ocular hypertension.

**Methods:** In 2 identical, multicenter, randomized, double-masked, 1-year clinical trials, patients were treated with 0.03% bimatoprost once daily (QD) (n=474), 0.03% bimatoprost twice daily (BID) (n=483), or 0.5% timolol maleate BID (n=241).

**Main Outcome Measures:** Diurnal intraocular pressure (IOP) at 8 AM, 10 AM, and 4 PM and safety variables (IOP was also measured at 8 PM at selected sites).

**Results:** Bimatoprost QD provided significantly lower mean IOP than timolol at every time of the day at each study visit (P<.001). This was also true for bimatoprost BID at most time points, but the efficacy was not as good as that of the QD regimen. At 10 AM (peak timolol effect) at month 12, the mean reduction in IOP from baseline was 7.6 mm Hg (30%) with bimatoprost and 5.3 mm Hg (21%) with timolol (P<.001). A significantly higher percentage of patients receiving bimatoprost QD (58%) than timolol (37%) achieved IOPs at or below 17 mm Hg at month 12; P<.001. The most common adverse effect with bimatoprost was hyperemia (significantly higher with bimatoprost QD than timolol; P<.001).

**Conclusions:** Bimatoprost QD provides sustained IOP lowering superior to timolol or bimatoprost BID and achieves low target IOPs in significantly more patients.

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**Bimatoprost** is a synthetic prostamide analogue that potently lowers intraocular pressure (IOP). Bimatoprost has been shown to help a substantially greater percentage of patients to achieve low IOPs (IOP≤17 mm Hg) than does timolol maleate.

Two large-scale, double-masked, phase 3 clinical (pivotal) trials were undertaken to evaluate the safety and efficacy of once- (QD) or twice-daily (BID) regimens of 0.03% bimatoprost ophthalmic solution (Lumigan; Allergan Inc, Irvine, Calif) compared with timolol maleate BID in patients with glaucoma or ocular hypertension. Interim safety and efficacy results were evaluated at 3 and 6 months without breaking study masking for the patients or the study investigators. These analyses demonstrated that bimatoprost QD was more effective in lowering IOP than was timolol throughout the day at all study visits through 6 months (P<.001). Moreover, a significantly higher percentage of patients treated with bimatoprost QD achieved low pressures (IOP≤17 mm Hg) than did patients treated with timolol (the highest P value for the comparison to timolol was .007). Bimatoprost BID was also more effective than timolol at most time points, but was slightly less effective than the QD regimen.

Because glaucoma is a chronic disease, it is important to evaluate the long-term efficacy and safety of new glaucoma medications. The present report describes the pooled 12-month results from the 2 pivotal clinical trials comparing bimatoprost with timolol.

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**METHODS**

**STUDY DESIGN**

Two multicenter, randomized, double-masked, parallel-group, active-controlled trials were conducted to compare the safety and efficacy of bimatoprost QD, bimatoprost BID, and timolol maleate BID. The study protocols were identical, and the data were pooled for analysis.

Both studies were conducted in accordance with the Declaration of Helsinki and the guidelines set forth by the International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for
human use and the United States Code of Federal Regulations CFR21. All investigators obtained appropriate institutional review board or ethics committee approval before initiating the study, and all patients provided written informed consent before any study-related procedures or changes in treatment.

patients

Key inclusion criteria included a diagnosis of primary open-angle glaucoma, chronic angle-closure glaucoma with patent iridotomy, pseudoxfoliative glaucoma, pigmented glaucoma, or ocular hypertension. Washout of ocular hypotensive medications occurred before the baseline visit, and patients were required to have a postwashout IOP of at least 22 mm Hg and no greater than 34 mm Hg and a best-corrected visual acuity of 20/100 or better in each eye. Washout periods ranged from 4 days to 4 weeks, depending on the medication. Parasympathomimetics and carbonic anhydrase inhibitors were washed out for 2 weeks, and topical β-blockers (alone or in combination) and topical prostaglandins were washed out for 4 weeks. Key exclusion criteria included any contraindication to topical β-blocker therapy, functionally significant visual field loss within the past year, filtering surgery within the past 6 months, or other intraocular surgery within the past 3 months. Women who were pregnant, nursing, planning a pregnancy, or of childbearing potential and not using a reliable form of contraception were also excluded.

treatment assignment and drug administration

At baseline, patients were randomly assigned in a 2:2:2 ratio to receive 0.03% bimatoprost QD, 0.03% bimatoprost BID, or 0.5% timolol maleate BID. The study sponsor generated the allocation sequence. The bimatoprost QD group received bimatoprost in the evening and a vehicle control solution in the morning to maintain the study mask. Medications were supplied in identical-appearing bottles that were color coded for use in the morning or the evening. Patients were instructed to self-instill their medication into both eyes at approximately 8 AM and 8 PM. On study visits, the morning dose was administered by the study investigator immediately after the first examination (at approximately 8 AM). Scheduled visits occurred before the study, at baseline (day 0), weeks 2 and 6, and months 3, 6, 9, and 12.

efficacy and safety variables

The primary outcome measure was diurnal IOP. Measurements were performed at 8 AM, immediately preceding the instillation of the morning dose of the study medication, and at 10 AM and 4 PM. Patients at selected sites (approximately 25% of all enrolled) also had IOP recorded at 8 PM (bimatoprost QD group, n=124; bimatoprost BID group, n=123; and timolol group, n=65). At month 9, IOP was recorded only at 8 AM and (at selected sites) 8 PM. Safety measures included adverse events, visual acuity, visual fields, blood pressure, heart rate, blood chemistry, iris pigmentation, and results of hematology, urinalysis, laser flare photometry, biomicroscopy, and ophthalmoscopy readings. The severity of adverse events was assessed using the following definitions as guidelines: mild indicates awareness of a sign or a symptom, but easily tolerated; moderate, enough discomfort to cause interference with usual activities; and severe, incapacitating, with the inability to work or to perform usual activities. Hyperemia was evaluated on the following scale: none, 0; trace, 0.5; mild, 1.0; moderate, 2.0; and severe, 3.0. To evaluate changes in iris pigmentation, investigator(s) at each site compared Polaroid photographs (Polaroid Corporation, Cambridge, Mass) of each patient's eyes from the baseline and follow-up visits. A color-calibration strip was photographed beside the eye to verify consistent photographic color processing. A reading center at the sponsor site (consisting of 2 evaluators) also evaluated all photographs in a masked fashion and obtained slightly lower but generally comparable results. At selected sites, laser-flare photometry readings (using a Kowa FM-50 photometer; Kowa Company, Ltd, Chuo-ku, Tokyo, Japan) were recorded before fluorescein instillation or pupil dilation.

analyses

All randomized patients were included in the efficacy analysis (intent-to-treat population), and for patients who discontinued before the month 12 visit, the last observed data were carried forward in the analysis for all subsequent time points. An intent-to-treat analysis with the last observation carried forward is the standard analysis for clinical studies of this type and is considered the most conservative analysis. It is much more difficult for a drug to appear to perform well in an intent-to-treat analysis with the last observation carried forward than in a per-protocol analysis because data from patients who did not receive study medications or who left the study early for any reason (including lack of efficacy) were kept in the efficacy analysis. Similar results (not shown) were obtained when the analysis used the per-protocol patient population without the last observations carried forward. Analysis of IOP used only data from the eye with the higher IOP at 8 AM at baseline (worse eye). If both eyes had the same IOP at baseline, the protocol required that the right eye be used. All patients who received at least 1 dose of study medication were included in the safety analyses.

Nominal categorical variables were analyzed using the Fisher exact test, the Pearson χ² test, or Cochran-Mantel-Haenszel methods. Ordinal categorical variables were analyzed by means of the Wilcoxon rank sum test. Continuous variables were analyzed using analysis of variance (ANOVA). We compared the frequency distributions of patients who had achieved desirable target IOP levels between groups. We performed the analysis for each target IOP at a given time point using the Pearson χ² test.

Tests of noninferiority and superiority were performed for the pairwise between-group comparisons of IOP at each time point. The α level for statistical significance was .05. Noninferiority of bimatoprost was claimed when the upper limit of the 95% confidence interval of the difference (bimatoprost minus timolol) was no greater than 1 mm Hg. Superiority was claimed when the upper limit of the confidence interval was less than 0 mm Hg. The power of each study was at least 0.85 to claim noninferiority of bimatoprost to timolol, based on a maximum difference of 1.5 mm Hg and using an estimate of variability (SD=4.052) from a prior study.² To test for an interaction of drug effect with patient race, the ANOVA was performed with the main effects of treatment group, race (black vs nonblack), and treatment-by-race interaction. The α level of significance for the interaction was set at .10 to accommodate a possible low power for this test.

We used the SAS computer program package (version 6.12 and version 7 on Unix; SAS Institute Inc, Cary, NC) for computation and analysis. All the variables were analyzed using SAS procedures (version 6.12 on Unix; SAS Institute Inc) with the exception of variables of adverse events, which were analyzed using version 8.

The sample-size estimate was based on the mean change in IOP from baseline. With 200 patients in each of the bima-
We found no statistically significant among-group differences in demographic characteristics, clinical diagnosis, or baseline IOP (Table 2). We also found no among-group difference in medical history or the use of concomitant medication that could affect IOP (eg, β-blockers). Medical histories did not designate any patients as low responders to β-blockers or prostaglandin agonists. Most patients were white, with brown or blue irides and a diagnosis of glaucoma. Approximately 18% of the study population was black. None of the black patients were from the Australian or New Zealand sites, and it is consequently unlikely that any Australian aborigines (who have a very low incidence of glaucoma) were included in the black subpopulation.

**IOP-LOWERING EFFICACY**

Baseline IOP was similar among the treatment groups throughout the day (Table 2). Bimatoprost QD provided IOP control that was superior to that of timolol at all time points and all follow-up visits throughout the 12-month study. During all times of the day at which post-treatment measurements were obtained, mean IOP ranged from 16.2 to 18.0 mm Hg with bimatoprost QD and from 18.2 to 20.0 mm Hg with timolol. As has been reported previously, bimatoprost BID did not perform as well as bimatoprost QD.3,4 The presentation of the efficacy results will focus on the data from the bimatoprost QD group, because this was the study regimen approved by regulatory authorities.

The peak effect for timolol typically occurs 2 hours after dosing. Therefore, in this report, the comparative response at each study visit will focus on the 10 AM IOP measurement on each follow-up visit (dosing occurred after the 8 AM examination at each visit). At 10 AM, mean±SEM IOP ranged from 16.4±0.2 to 17.0±0.2 mm Hg with bimatoprost QD and from 18.2±0.2 to 19.0±0.2 mm Hg with timolol (Figure 2). The difference between the bimatoprost QD and timolol groups was statistically significant at every follow-up visit (P<.001). Mean IOP reductions from baseline were also significantly greater with bimatoprost QD than with timolol at this morning peak throughout the 12-month treatment period (P<.001). Mean IOP reductions ranged from 7.6 to 8.3 mm Hg (30.2%-32.9%) in the bimatoprost QD group and from 5.1 to 5.8 mm Hg (20.4%-23.3%) in the timolol group. The mean IOP reduction from baseline consistently ranged from 1.8 to 2.1 mm Hg greater in the bimatoprost QD group than in the timolol group at the 10 AM measurement. The decrease from baseline IOP was up to 8.8 mm Hg in the bimatoprost QD group compared with 6.5 mm Hg in the timolol group (across all times of day and all study visits).

Significantly higher percentages of patients achieved low IOP levels with bimatoprost QD than with timolol (Figure 3). The 10 AM measurement at month 12 revealed that target IOPs at or below 17 mm Hg were achieved by 57.6% of the bimatoprost QD group compared with 36.5% of the timolol group (P<.001). Pressures at or below 15 mm Hg were achieved by 30.6% of the bimatoprost QD group and 15.8% of the timolol group (P<.001). Patients in the bimatoprost QD group were up to 2½ times more likely than those in the timolol group...
to achieve low pressures that were at or below 12, 13, 14, 15, 16, or 17 mm Hg.

Bimatoprost QD was also superior to timolol in maintaining a low IOP throughout the day. As mentioned in the two preceding paragraphs, bimatoprost QD produced significantly lower mean IOPs than did timolol at every time of the day at each follow-up visit throughout the 12-month treatment period (P<.001). The overall diurnal mean IOP (average of all measurements at a given time from all follow-up visits) was significantly lower in the bimatoprost QD group than the timolol group at each time of day. Throughout the day, overall mean IOP in the bimatoprost QD group was approximately 2 mm lower than the overall mean IOP in the timolol group (P<.001; Figure 4). The IOP-lowering efficacy of the single evening dose of bimatoprost was still profound 24 hours after dosing. At the 8 PM measurements, mean±SEM IOP ranged from 16.2±0.3 to 17.2±0.3 mm Hg with bimatoprost QD (n=124) compared with 18.2±0.5 to 20.0±0.6 mm Hg with timolol BID (n=65).

A subgroup analysis by race demonstrated that bimatoprost was significantly more effective than timolol in lowering IOP in both black and nonblack patients. Bimatoprost lowered IOP to the same extent in both black and nonblack patients, while timolol was notably less effective in blacks than in nonblacks (by up to approximately 2 mm). The statistical validity of this was identified from the significant treatment-by-race interaction based on the analysis of variance model for repeated measures with the fixed effects of treatment, time, race (black and nonblack), and treatment-by-race interaction. When either mean IOP or mean change from baseline IOP was analyzed for each time of day across all study visits, the between-group statistical comparison for iris color is for the distribution of dark vs light irides.

The between-group statistical comparison for iris color is for the distribution of dark vs light irides.
individual trials were evaluated separately. For example, in each trial and in the pooled data, diurnal mean IOP at month 12 was consistently 2 to 3 mm Hg lower with bimatoprost QD than with timolol throughout the day (Figure 5).

SAFETY AND TOLERABILITY

We found a low rate of discontinuations due to adverse events. All 3 treatment regimens were safe and well tolerated. The most common adverse effects associated with bimatoprost were conjunctival hyperemia and eyelash growth.

Other potentially treatment-related adverse events that occurred in more than 5% of the bimatoprost QD group are listed in Table 3 and included eye pruritus, eye dryness, eye burning, eyelid pigmentation, foreign-body sensation, eye pain, and visual disturbance. For some of these adverse events, we found a significantly higher incidence in the bimatoprost QD group than in the timolol group. However, no statistically significant difference was found between the bimatoprost QD and timolol groups in the number of reports of eye pain, visual disturbance, and burning sensation in the eye. Patients in the bimatoprost BID group had a higher incidence of hyperemia, eyelash growth, eyelid pigmentation, and eye pain than did patients in the bimatoprost QD group (P<.01). Most treatment-related adverse events were mild in severity.

Assessment of the hyperemia findings were confounded by the fact that trace or greater conjunctival hyperemia was present at baseline (before the initial administration of the study medication) in 25.1% of the patients in the bimatoprost QD group and in 17.8% of the patients in the timolol group. Mean scores of conjunctival hyperemia (worse severity of the eyes) were low (in the trace range) in the bimatoprost QD treatment group and remained low throughout the study (Figure 6). Only 5.3% of patients experienced greater than a 1-U (mild) increase in hyperemia during this 12-month study. Only 3.4% of the patients in the bimatoprost QD group, 5.6% of those in the bimatoprost BID group, and 0.4% of those in the timolol group discontinued from the study owing to hyperemia (P=.01; bi-

Table 3. Treatment-Related Adverse Events*

<table>
<thead>
<tr>
<th>Event</th>
<th>Bimatoprost QD (n = 474)</th>
<th>Bimatoprost BID (n = 483)</th>
<th>Timolol Maleate (n = 241)</th>
<th>Bimatoprost QD vs Timolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival hyperemia</td>
<td>212 (44.7)</td>
<td>271 (56.1)</td>
<td>32 (13.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eyelash growth</td>
<td>202 (42.6)</td>
<td>259 (53.6)</td>
<td>12 (5.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>69 (14.6)</td>
<td>85 (17.6)</td>
<td>8 (3.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Eye dryness</td>
<td>38 (8.0)</td>
<td>56 (11.6)</td>
<td>5 (2.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Burning sensation in the eye</td>
<td>33 (7.0)</td>
<td>32 (6.6)</td>
<td>25 (10.4)</td>
<td>.17</td>
</tr>
<tr>
<td>Eyelid pigmentation</td>
<td>26 (5.5)</td>
<td>55 (11.4)</td>
<td>1 (0.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>26 (5.5)</td>
<td>48 (9.9)</td>
<td>5 (2.1)</td>
<td>.03</td>
</tr>
<tr>
<td>Eye pain</td>
<td>24 (5.1)</td>
<td>45 (9.3)</td>
<td>8 (3.3)</td>
<td>.29</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>24 (5.1)</td>
<td>37 (7.7)</td>
<td>11 (4.6)</td>
<td>.14</td>
</tr>
</tbody>
</table>

*QD indicates once daily; BID, twice daily.
matoprost QD vs timolol). The median time to onset of hyperemia was 14 days after the initiation of therapy, and in most cases it began within the first 6 weeks. No patients receiving bimatoprost QD discontinued the study because of conjunctival hyperemia after month 6.

Laser-flare photometry measurements (a common measure of ocular inflammation) of a subset of 310 patients (124 in the bimatoprost QD group, 123 in the bimatoprost BID group, and 63 in the timolol group) demonstrated that there were no significant differences among the treatment groups in mean laser-flare photometry readings or in mean changes from baseline. In addition, we found no increase in flare readings in those patients in whom conjunctival hyperemia developed. In fact, after 12 months of bimatoprost QD treatment, mean laser-flare photometry readings were lower in patients who had a mild or greater increase in conjunctival hyperemia (7.67 photon counts/ms) compared with those in patients who had no change, a trace increase, or a decrease in hyperemia (9.26 photon counts/ms) (Figure 7); however, this difference was not statistically significant (P = .37).

Changes in iris pigmentation, determined by the results of the masked investigators’ evaluation of the photographs, were reported in 7 (1.5%) of the 474 patients in the bimatoprost QD group, 9 (1.9%) of the 483 patients in the bimatoprost BID group, and no patients in the timolol group. Generally comparable findings were obtained by the sponsor’s reading center.

The incidence of adverse events leading to discontinuation was comparably low in the bimatoprost QD and timolol groups. In the bimatoprost QD treatment group, 8.4% of patients discontinued owing to adverse events, compared with 5.0% in the timolol group (P = .09). The discontinuation rate due to ocular adverse events was 5.3% in the bimatoprost QD group and 1.7% in the timolol group. This difference was statistically significant (P = .02), exclusively because of the statistically significant difference in the number of patients who discontinued owing to hyperemia (3.4% in the bimatoprost QD group and 0.4% in the timolol group; P = .01). We found no between-group difference in the number of patients who dis-

continued because of any other adverse event. In the bimatoprost BID treatment group, 14.7% of patients discontinued because of adverse events (P = .003 compared with bimatoprost QD).

No clinically significant changes in results of ophthalmoscopy, laser-flare photometry readings, visual acuity, visual fields, or systemic safety variables were found with any treatment regimen.

The pooled 1-year results of the 2 pivotal phase 3 trials clearly demonstrated that bimatoprost QD was superior to timolol in long-term IOP reduction. Significantly higher percentages of patients achieved low pressures with bimatoprost QD, and IOP was controlled throughout the day. The efficacy of bimatoprost QD was sustained throughout the 1-year study. The mean reduction from baseline IOP in the bimatoprost QD group was very consistent (range, 30%-33%) at follow-up visits through 1 year of treatment.

Controlling IOP is critical to slowing the progression of glaucomatous damage in patients with glaucoma or ocular hypertension. Elevated IOP is the single most important risk factor for open-angle glaucoma, and numerous studies have found that reducing IOP decreases the risk for visual field loss in patients with glaucoma. A recent analysis by the Advanced Glaucoma Intervention Study group demonstrated that after surgery to reduce IOP, patients who consistently had IOPs less than 18 mm Hg at every clinic visit during the 6-year follow-up showed mean changes in visual fields close to 0. In these patients, the mean IOP was very low (12.3 mm Hg), suggesting that lower IOPs result in greater patient benefit. Reductions in IOP of 30% or greater have also been shown to significantly reduce the rate of glaucomatous progression in patients with normal-tension glaucoma. Even in patients without evidence of optic disc cupping, reduction of an elevated IOP can be beneficial in delaying the onset of early glaucomatous damage. Therefore, a goal of glaucoma therapy should be the
achievement and maintenance of target IOPs that are low enough to minimize glaucomatous progression. On the basis of the superior IOP-lowering efficacy of bimatoprost QD demonstrated in the present study, long-term bimatoprost QD treatment may reasonably be assumed to provide greater protection for the visual field than does timolol in patients with glaucoma or ocular hypertension. The greater ability of bimatoprost to help patients reach IOP levels more consistently below 18 mm Hg should prove particularly beneficial.

A recent study by Asrani and colleagues reported that large fluctuations in diurnal IOP are an independent risk factor for the progression of glaucomatous damage. The results of the present study show that bimatoprost QD effectively controls IOP fluctuations throughout the day that could otherwise increase the risk for further optic nerve damage.

Numerous studies have reported significant differences between black and nonblack populations in the prevalence of glaucoma and the response to treatment. Population-based studies have reported that glaucoma is 4 to 6 times more prevalent in black than in non-black populations and that glaucoma is 6 to 8 times more likely to lead to blindness in black than in nonblack populations. The reasons for the greater prevalence and visual field loss in black populations are not yet known. The results of the present study demonstrated that bimatoprost QD reduces IOP as effectively in black as in nonblack patients, and that bimatoprost QD provides IOP lowering superior to that of timolol across both of these patient populations.

Throughout 1 year of treatment, bimatoprost QD was safe and well tolerated. The most common adverse effect, conjunctival hyperemia, was generally well tolerated and mild in severity. In our experience, hyperemia can resolve after 2 to 4 weeks of treatment. The lack of any correlation between hyperemia and laser-flare photometry readings indicates that there was no association with intraocular inflammation and confirms the general finding that this adverse effect does not represent a significant clinical safety concern. The investigating physicians reported an increase in iris pigmentation in only 1.5% of the patients in the bimatoprost group treated for 12 months. By comparison, in the phase 3 clinical trials of latanoprost in which iris pigmentation changes were evaluated at a reading center, the incidence of increased iris pigmentation ranged from 10.9% to 22.9% of patients treated with latanoprost QD for 12 months. These results suggest that iris pigmentation changes may occur less frequently with bimatoprost than with latanoprost. However, given the different techniques used in the studies of these 2 drugs and the variation in the ability of investigators to detect iris pigment changes, a long-term comparison of bimatoprost with latanoprost using a single method will be needed to evaluate this issue more thoroughly.

Bimatoprost BID was associated with a significantly higher incidence of certain adverse events than was bimatoprost QD. This, along with the greater efficacy of the QD regimen, supports the once-daily use of this drug.

We found 0.03% bimatoprost QD to be clinically and statistically superior to 0.5% timolol maleate BID in lowering IOPs in patients with glaucoma or ocular hypertension. Significantly more patients achieve very low target pressures with bimatoprost QD than with timolol maleate BID. Bimatoprost QD provides potent IOP control throughout the day and is safe and well tolerated. The efficacy of bimatoprost QD is sustained through at least 1 year of treatment.

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REFERENCES


CME Announcement

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CME from JAMA/Archives will be suspended between July and December 2002. Beginning in early 2003, we will offer a new online CME program that will provide many enhancements:

- Article-specific questions
- Hypertext links from questions to the relevant content
- Online CME questionnaire
- Printable CME certificates and ability to access total CME credits

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