·Clinical Research·

Bimatoprost/timolol fixed combination (BTFC) in patients with primary open angle glaucoma or ocular hypertension in Greece

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Abstract

• AIM: To evaluate the efficacy and tolerability of the fixed combination of bimatoprost 0.03% and timolol 0.5% (BTFC) in patients in Greece with primary open angle glaucoma (POAG) or ocular hypertension (OHT) whose previous therapy provided insufficient lowering of intraocular pressure (IOP).

• METHODS: A multicenter, prospective, open-label, non-interventional, observational study of the use of BTFC in clinical practice was conducted at 41 sites in Greece. The primary endpoint was the reduction in IOP from baseline at study end, approximately 12wk after initiation of BTFC therapy.

• RESULTS: A total of 785 eligible patients were enrolled in the study and 97.6% completed the study. The mean ±SD IOP reduction from baseline at 12wk after initiation of BTFC was 6.3±2.8 mm Hg (n=764; P<0.001). In patients (n=680) who replaced their previous IOP-lowering monotherapy (a single drug, or a fixed combination of 2 drugs in a single ophthalmic drop) with once-daily BTFC, the mean±SD IOP reduction from baseline at 12wk was 6.2±2.8 mm Hg (P<0.001). IOP was reduced from baseline in 99.2% of patients, and 58.0% of patients reached or exceeded their target IOP. Substantial mean IOP reductions were observed regardless of the previous therapy. BTFC was well tolerated, with 96.0% of patients who completed the study rating the tolerability of BTFC as "good" or "very good." Adverse events were reported in 8.3% of patients; only 0.6% of patients discontinued the study due to adverse events.

• CONCLUSION: In clinical practice in Greece, BTFC is well tolerated and effectively lower the IOP in patients with POAG or OHT who requires additional IOP lowering on their previous therapy.

• **KEYWORDS:** fixed combination; glaucoma; intraocular pressure; ocular hypertension; primary open angle glaucoma; prostaglandin; prostamide; timolol
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INTRODUCTION

Increased intraocular pressure (IOP) is known to be a cardinal risk factor for the development of primary open angle glaucoma (POAG). There are a number of effective pharmacologic approaches to the treatment of this condition. Along with the Early Manifest Glaucoma Trial [1], which demonstrated the importance of controlling IOP in the progression of the disease, the recently published Canadian Glaucoma Study [2] showed that mean IOP was highly significantly associated with disease progression, with every 1 mm Hg adding a 19% increased risk of progression. For the treatment of patients with advanced-stage glaucoma, the Advanced Glaucoma Intervention Study [3] showed that consistently limiting the IOP to a maximum of 18 mm Hg while limiting IOP fluctuation prevents additional structural damage and slows further visual field loss.

Compliance with medical therapy is a major issue, since glaucoma only rarely causes tangible symptoms before the onset of irreversible damage [4]. Medication for reducing IOP is often taken irregularly, especially when patients experience side effects or are required to apply eye drops several times per day [5]. Measures that may improve compliance, such as once-daily dosing [6], combining 2 or more medications in 1 drop [7], as well as a tolerable formulation, are important because better compliance is associated with better visual outcomes[8-9].

GANfort® (Allergan, Inc., Irvine, CA, USA), a fixed combination of bimatoprost 0.03% and timolol 0.5% (BTFC)[10-12], is indicated for reduction of IOP in patients with POAG or ocular hypertension (OHT) who are insufficiently

responsive to monotherapy. The primary objective of this observational study in Greece was to assess the efficacy of BTFC in reducing IOP in patients who were treated with BTFC in clinical practice.

SUBJECTS AND METHODS

This prospective, open-label, non-interventional, multicenter, observational study was designed to collect data on the use of BTFC in patients with POAG and/or OHT in a routine clinical setting. The decision to commence BTFC therapy resided with the treating physician. Subsequent care and follow-up were also at the discretion of the participating physicians and reflected their clinical judgment and the local standard of medical care.

The study protocol was approved by an Institutional Review Board or Administrative Council at the participating hospital sites and by the National Organization for Medicines. The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the section of the EU directive 2001/20/EC on non-interventional studies. All patients provided written informed consent prior to enrollment. No stipends were provided for study participation.

A total of 1250 eligible patients diagnosed with POAG or OHT were planned to be enrolled in the study at approximately 57 sites (7 hospital sites and 50 office-based practice physicians) across Greece during a 6-month recruitment period. The planned duration of the study for each patient was 12wk, which was deemed adequate for the assessment and record of subjects' response to therapy with BTFC therapy in daily clinical practice.

Subjects were free to discontinue their participation in the study at any time during its conduct and for any reason, without any impact on their future medical care and therapy.

Subjects Patients included in the study were adults age 18-80y, with a diagnosis of POAG or OHT, who were inadequately controlled on a monotherapy (a single drug, or a fixed combination of 2 drugs in a single ophthalmic drop) prior to BTFC treatment. Patients who were beginning BTFC treatment, or who had begun BTFC treatment within the previous 2wk, were eligible to participate in the study if data were available concerning their ocular status prior to the initiation of BTFC treatment.

Patients with any contraindication detailed within the GANfort summary of product characteristics, or who had participated in any interventional study within the previous 3mo, were ineligible for the study. Women who were pregnant or breast-feeding were also excluded.

Study Visits and Outcome Measures At the baseline visit (visit 1), patients were enrolled and began BTFC therapy. Baseline data collected included demographics, previous treatment for POAG/OHT, and IOP before initiation of BTFC therapy. For patients who had started BTFC therapy within the preceding 2wk, the IOP before initiation of BTFC therapy was obtained from the medical chart. Follow-up data were recorded at visits approximately 4-6wk (visit 2) and 12wk (visit 3) after initiation of BTFC therapy, scheduled according to normal clinical practice. The method of tonometry and the time of day for IOP measurements were not standardized.

The primary endpoint was the reduction in IOP from baseline to the final study visit at approximately 12wk. Secondary endpoints included the reduction in IOP from baseline to visit 2 and from visit 2 to visit 3, patient achievement of target IOP on BTFC therapy, patient and physician assessments of tolerability of treatment with BTFC, physician assessments of patient adherence to BTFC treatment compared with previous therapy, and adverse events reported by patients or observed by the physician. The target IOP for each patient was determined by the physician. The tolerability of treatment in the opinion of patients and physicians was judged as very good, good, moderate, or poor. Patient adherence to the prescribed therapy was judged by the physician to be better, equal, or worse than adherence to the previous therapy.

Statistical Analysis Descriptive statistical analysis of the study data was performed using SPSS v.20 statistical software (IBM, Armonk, New York, USA). All statistical tests used a 2-sided α level of 0.05.

For patients with both eyes enrolled and treated with BTFC, the analysis used the mean of the IOP readings in both eyes as the patient's IOP. For patients with 1 eye eligible and treated with BTFC, the analysis used the IOP in the BTFC-treated eye as the patient's IOP. Change in IOP between visits was evaluated with the Wilcoxon signed-rank test for related samples. All analyses used observed values in the full analysis set (FAS) of all patients who enrolled in the study and met all eligibility criteria for the study, regardless of whether the patients completed the study.

RESULTS

A total of 793 patients were enrolled in the study at 41 investigational sites (5 hospital-based and 36 office-based ophthalmologists) covering the major prefectures of Greece. Slightly more than half of the participating hospitals (56.1%, 23/41) are located outside Attica and accounted for 60.7% (481/793) of the patient enrollment. Overall, 99.0% (785/793) of enrolled patients met the eligibility criteria and comprised the FAS analyzed in this report. The 12-week study was completed by 97.6% (766/785) of patients in the FAS. The main reason for patient discontinuation from the study was loss to follow-up (Table 1).

Slightly more females (53.1%) than males were enrolled in the study, and most of the study participants were diagnosed with POAG in both eyes (Table 2). The mean age of the study population was 68.0 ±9.3y. As detailed in Table 3, 57.7% of the study participants had been previously treated

Table 1 Patient disposition

Parameters	*n*	%
Enrolled	793	100
Did not meet study eligibility criteria (excluded from analysis)[1]	8	1.0
Met eligibility criteria and included in statistical analysis (FAS)	785	99.0
Continued in study at visit 2 (4-6wk after BTFC initiation) (FAS)	781	99.5
Completed study (12wk after BTFC initiation) (FAS)	766	97.6
Discontinued from study (FAS)	19	2.4
Reason for discontinuation		
Loss to follow-up	13	1.6
Adverse event	5	0.6
Other (personal reason of patient)	1	0.1

[1]Eight patients were excluded from the FAS because they were older than 80y and did not meet the age criteria for study eligibility. BTFC: Bimatoprost/timolol fixed combination; FAS: Full analysis set.

Table 2 Baseline characteristics of study population (FAS) *n*=785

Characteristic	Study population
Age (a)	
Mean (SD)	68.0 (9.3)
Median	70.0
Range	22.2-80.9
Gender, *n* (%)	
M	368 (46.9)
F	417 (53.1)
Ocular diagnosis, *n* (%)	
POAG (both eyes)	627 (79.9)
OHT (both eyes)	97 (12.4)
POAG and OHT (both eyes)	13 (1.7)
POAG or OHT in 1 eye	45 (5.7)
POAG/OHT (1 eye each)	3 (0.4)

OHT: Ocular hypertension; POAG: Primary open angle glaucoma; FAS: Full analysis set.

with a prostaglandin analog/prostamide, 14.9% with a β-blocking agent, 7.3% with a timolol combination product, 12.1% with a carbonic anhydrase inhibitor, 7.5% with an α-agonist, and 0.5% with a parasympathomimetic prior to beginning study treatment. The most commonly used prostaglandin analog was latanoprost (35.3%) followed by travoprost (15.8%); timolol was the most commonly used β-blocking agent (11.2%). Among the 431 patients with available data on the duration of previous treatment, the median duration of previous treatment for POAG/OHT was 10mo.

Previous IOP-lowering medical therapy was usually discontinued when BTFC was initiated. The replacement of previous therapy with BTFC was documented for 88.4% (694/785) of patients. In the remaining patients, either the previous therapy was discontinued but the physician did not record the discontinuation on the case report form

Table 3 Previous therapy for primary open angle glaucoma or ocular hypertension (FAS) *n*=785

Previous therapy	*n*	%
α_2-adrenergic agonist	59	7.5
Brimonidine	59	7.5
β-adrenergic antagonist	117	14.9
Timolol	88	11.2
Other β-blocker	29	3.7
Carbonic anhydrase inhibitor	95	12.1
Brinzolamide	41	5.2
Dorzolamide	54	6.9
Fixed combination including timolol	57	7.3
Brimonidine/timolol	10	1.3
Brinzolamide/timolol	4	0.5
Dorzolamide/timolol	24	3.1
Latanoprost/timolol	13	1.7
Pilocarpine/timolol	1	0.1
Travoprost/timolol	5	0.6
Parasympathomimetic	4	0.5
Pilocarpine	4	0.5
Prostaglandin analog/prostamide	453	57.7
Bimatoprost	39	5.0
Latanoprost	277	35.3
Prostaglandin (unspecified)	13	1.7
Travoprost	124	15.8

FAS: Full analysis set.

Table 4 Reasons for changing therapy to bimatoprost/timolol fixed combination (FAS) *n*=785

Reason	*n*	[1]%
Insufficient IOP control	691	88.1
Progression of glaucoma-related damage	197	25.1
Insufficient tolerability	81	10.3
Lack of compliance	65	8.4
Glaucoma-related changes observed (in patients with OHT)	44	5.6
[2]Other	4	0.5
[3]Unknown	1	0.1

[1]Percentages do not sum to 100% because for many patients, more than 1 reason was recorded; [2]Reasons recorded as "other" on the case report form were allergic reaction, intolerance, hyperemia, and Fuchs' dystrophy; [3]Data missing for 1 patient. IOP: Intraocular pressure; OHT: Ocular hypertension; FAS: Full analysis set.

appropriately (the physician did not indicate that the therapy was ongoing, but also did not indicate a stopping date), or BTFC was added to previous therapy. The most commonly reported reason for initiating BTFC therapy was insufficient IOP control (Table 4). Other reported reasons were progression of glaucoma-related damage, insufficient tolerability, lack of compliance, and glaucoma-related changes in patients with OHT. Most patients (93.9%, 737/785) were treated with BTFC in both eyes.

Mean baseline IOP on a per-patient basis was 22.1±3.2 mm Hg and on a per-treated eye basis was 22.1±3.5 mm Hg for right

Table 5 Intraocular pressure (FAS)

Parameters (mm Hg)	*n*	Mean	SD	Med	Min	Max	[2]*P*
Descriptive statistics of IOP at each study visit							
Baseline visit	785	22.1	3.2	22.0	15.0	39.0	
Visit 2 (4-6wk)	781	16.4	2.4	16.5	8.0	28.5	
Visit 3 (12wk)	[1]764	15.7	2.2	16.0	9.0	25.0	
Reduction in IOP between baseline and visit 2							
IOP change (baseline-visit 2)	781	5.7	2.7	5.5	-2.0	25.0	<0.001[a]
Percentage (%) IOP change	781	25.2	10.0	25.0	-13.3	67.6	
[1]Reduction in IOP between visit 2 and visit 3							
IOP change (visit 2-visit 3)	764	0.6	1.3	0.5	-2.5	13.0	<0.001[a]
Percentage (%) IOP change	764	3.4	7.4	2.9	-21.77	46.4	
[1]Reduction in IOP between baseline and visit 3							
IOP change (baseline-visit 3)	764	6.3	2.8	6.0	-0.5	23.0	<0.001[a]
Percentage (%) IOP change	764	28.0	10.2	28.1	-3.3	62.2	

[1]Two patients were excluded from the analysis because they had discontinued study treatment at visit 3; [2]Wilcoxon signed-rank test; [a]Statistically significant; IOP: Intraocular pressure; Max: Maximum; Med: Median; Min: Minimum; SD: Standard deviation; FAS: Full analysis set.

eyes and 21.9±3.4 mm Hg for left eyes. For study eyes with corneal pachymetry data, the baseline corneal thickness was 542.9±30.8 μm in right eyes (*n*=199) and 544.3±31.1 μm in left eyes (*n*=196). Among patients with available data, the median duration from POAG/OHT diagnosis until initiation of BTFC therapy was 1.0y [mean duration (±SD) 2.0±2.7y, *n* =479], and the mean IOP target as determined by the treating physician was 15.9±1.7 mm Hg (*n* =378). BTFC was usually dosed 1 drop/day in the evening in each treated eye, with the dosing regimen remaining constant throughout the study. At the week 12 visit, approximately 89% of study eyes were receiving once-daily BTFC administration, with the remainder receiving twice-daily BTFC administration, and the dosing of BTFC was once-daily in the evening for approximately 72% of study eyes.

BTFC lowered mean IOP to 16.4±2.4 mm Hg after 4-6wk of therapy (*P* <0.001 versus baseline) and to 15.7±2.2 mm Hg after 12wk of therapy (*P* <0.001 versus baseline); the corresponding percentage reductions in IOP were 25.2% and 28.0%, respectively (Table 5). The mean reduction in IOP from baseline at 12wk was similar for patients receiving once-daily or twice-daily BTFC administration, 6.3±2.8 mm Hg and 6.5 ±3.2 mm Hg, respectively. In the patients with documented replacement of all previous therapy with BTFC, mean IOP was reduced from 22.1±3.2 mm Hg at baseline to 16.5±2.3 mm Hg after 4-6wk of therapy (*P*<0.001 versus baseline) and to 15.8±2.2 mm Hg after 12wk of therapy (*P*<0.001 versus baseline). The mean reduction in IOP from baseline for the 680 patients who replaced all previous therapy with once-daily BTFC was 5.6±2.6 mm Hg (*P* <0.001 versus baseline) at 4-6wk and 6.2±2.8 mm Hg (*P* <0.001 versus baseline) at 12wk.

There was a statistically significant difference in IOP reduction among patient cohorts based on previous treatment

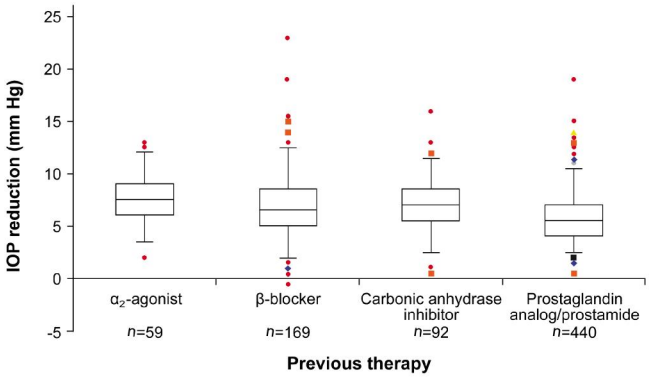

Figure 1 Distribution of IOP reduction by previous treatment

Boxes: 25th, 50th, and 75th percentiles; whiskers: 5th and 95th percentiles. Outliers: red circle, *n* =1; orange square, *n*=2; yellow triangle, *n*=3; blue diamond, *n*=4; gray circle, *n*=7; black square, *n*=13. β-blocker agents include combination products.

(*P* <0.001, Kruskal-Wallis test). The distribution of IOP reduction from baseline at visit 3 (12wk after initiation of BTFC) for patient subgroups based on previous treatment is shown in Figure 1. Although IOP decreased in all cohorts after initiation of BTFC treatment, the mean IOP reduction was largest (7.8 ±1.8 mm Hg) in the cohort of patients previously treated with a parasympathomimetic and smallest (5.8±2.6 mm Hg) in the cohort of patients previously treated with a prostaglandin analog/prostamide. However, it should be noted that conclusions concerning the difference in IOP lowering between these cohorts cannot be drawn because only 4 patients were previously treated with a parasympathomimetic. IOP reductions in the patients previously treated with a parasympathomimetic were 5.5, 7.0, 9.0, and 9.5 mm Hg.

On physician evaluation at 12wk, the majority of patients (58.0%; 444/766) had reached or exceeded the physician-determined target IOP, and an additional 41.3% (316/766) of

patients had experienced a reduction in IOP but had not reached the target IOP. Only 0.8% (6/766) of patients had no change in IOP after initiation of BTFC therapy. No patients had an increase in IOP. At week 12, the physicians rated the tolerability of BTFC therapy as "good" or "very good" for 97.4% (746/766) of patients, and 96.0% (735/766) of the patients themselves rated the tolerability of BTFC therapy as "good" or "very good". In the judgment of the physicians, the majority of study participants (59.8%; 458/766) exhibited better adherence to therapy with BTFC compared with the previous therapy, 40.1% (307/766) had equal adherence, and only 0.1% (1/766) had poorer adherence to BTFC compared with the previous medication.

Adverse Events and Adverse Drug Reactions No serious adverse events were reported in the FAS population (Table 6). A total of 82 non-serious adverse events were reported in 65 patients (8.3%); 66 adverse events were reported in 54 of 697 patients receiving 1 drop daily therapy (7.7%) compared with 16 adverse events in 11 of 83 patients receiving 2 drops daily therapy (13.3%). Almost all adverse events (81/82) were assessed as study drug-related by the investigators; 28.0% (23/82) were considered definitely related, 59.8% (49/82) were considered probably related, and 11.0% (9/82) were considered possibly related to study drug.

The most commonly reported adverse events were ocular, and 7.4% of the study participants (58/785) had 1 or more ocular adverse events. The only adverse events with an incidence ⩾1% were conjunctival hyperemia (2.2%), ocular hyperemia (2.0%), eye irritation (1.4%), and eye pruritus (1.1%). In severity grading, 35.4% (29/82) of reported adverse events were mild, 53.7% (44/82) were moderate, and 11.0% (9/82) were severe.

Table 6 Incidence of adverse events (FAS) *n* (%)

Event	Patients with ⩾1 event	No. of events
Any AE	65 (8.3)	82
Non-serious AE	65 (8.3)	82
Serious AE	0 (0.0)	0
Non-serious adverse drug reaction	64 (8.17)	81
Serious drug reaction	0 (0.0)	0

AE: Adverse event; FAS: Full analysis set.

DISCUSSION

Prostaglandin analogs and prostamides are among the most frequently used therapies for raised IOP [13]. The prostamide bimatoprost (Lumigan®, Allergan, Inc., Irvine, CA, USA) reduces IOP *via* 2 mechanisms of action, by increasing both uveoscleral drainage and trabecular meshwork outflow [14]. β-blockers, which have been used for IOP lowering for many years and are still among the first-line agents according to European Glaucoma Society guidelines [4], reduce IOP *via* inhibition of aqueous humor production [15]. It is therefore logical to combine both agents, with their complementary pathways of action, to treat the many patients who cannot be managed satisfactorily with a single drug therapy. Many patients eventually require multidrug therapy in order to control IOP [16]. However, use of 2 separate products is cumbersome, and many patients do not wait several minutes between administration of the individual products, as required to prevent washout [17]. A fixed combination of 2 active ingredients in a single formulation could provide the benefit of combination therapy more conveniently, may be a regimen with which the patient can more readily comply, and could further benefit patients with a reduction in exposure to potentially harmful preservatives[18].

Randomized controlled trials (RCTs) provide high-quality evidence of efficacy and safety. In a 3-month RCT in patients with glaucoma or OHT at sites in the United States and Canada, once-daily BTFC reduced IOP better than monotherapy with once-daily bimatoprost or twice-daily timolol, and the fixed combination was better tolerated than bimatoprost alone [11]. Once-daily BTFC demonstrated efficacy similar to an unfixed combination of once-daily bimatoprost and twice-daily timolol, and better tolerability, in a 3-week RCT conducted in the United States, Canada, Austria, and Germany [10]. These trials demonstrated the efficacy and safety of BTFC compared with its component medications. Subsequent RCTs conducted in Europe further showed that BTFC reduces IOP more effectively than fixed combinations of latanoprost and timolol[19-20] or travoprost and timolol[21] in patients with open-angle glaucoma.

Observational studies provide important information concerning the effectiveness of treatment in clinical practice. Pfennigsdorf *et al* [22] recently published a combined analysis of 5 observational studies in Germany [23], Austria, France, Switzerland, and the Netherlands of the safety and tolerability of BTFC in 5556 patients with POAG or OHT who were treatment-naïve or previously treated, and who typically began BTFC treatment because previous therapy had provided insufficient IOP lowering. Patients usually discontinued previous treatment when initiating BTFC, but in some cases BTFC was administered adjunctively [23]. The reduction in IOP over a 12-week period in the combined analysis population was 5.4 mm Hg, and adverse events were reported in 9.7% of patients. In comparison, the reduction in IOP over a 12-week period in this Greek observational study was slightly greater (6.3 mm Hg), and the incidence of adverse events (8.3%) was slightly lower. Another 12-week observational study of use of BTFC in patients with POAG or OHT who had inadequate IOP control and required a medication change was conducted in Germany [24]. In that study, the mean reduction in IOP from baseline at 12wk after initiation of BTFC treatment was less (4.6 mm Hg), but

patients were receiving as many as 3 IOP-lowering formulations at baseline, and all previous medications were discontinued when the patients began BTFC treatment[24].

This study was not designed to rigorously evaluate once-daily versus twice-daily dosing of BTFC. In subgroup analysis, no additional benefit in terms of IOP reduction was noted for patients receiving more than 1 drop per day, however, the incidence of adverse events appeared to be higher in patients receiving 2 drops per day than in those receiving the licensed dose of 1 drop daily (13.3% versus 7.7%). Once-daily dosing of BTFC is recommended, and caution should be exercised with increased dosing because of the probable increased risk of adverse events.

The current study has limitations inherent with all observational studies. There was no washout period prior to commencing BTFC, BTFC dosing was not standardized, and clinic visits occurred as per clinical practice. Incomplete case report forms made it impossible in some cases to determine whether BTFC was used alone or was added to previous therapy. Also, surgical or nonmedical treatments for IOP during the study period were not recorded. The study was of relatively short duration, sufficient to demonstrate a reduction in IOP, but insufficient to assess disease progression or long-term safety.

In summary, in this study BTFC was shown to be effective in lowering IOP by a mean of 6.3 mm Hg in Greek patients who needed a change in therapy, most often because of insufficient IOP control or progression of glaucoma-related damage on previous therapy. BTFC was well tolerated with adverse events reported in only 8.3% of patients and only 0.6% of patients discontinuing the study due to adverse events.

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Conflicts of Interest: Rotsos TG, None; **Kliafa VG,** Employee of Nexus Medicals S.A.; **Asher KJ,** Employee of Allergan Holdings Limited; **Papaconstantinou D,** None.

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