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A 1-year study to compare the efficacy and safety of once-daily travoprost 0.004%/timolol 0.5% to once-daily latanoprost 0.005%/timolol 0.5% in patients with open-angle glaucoma or ocular hypertension

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PURPOSE. *The objective of the study was to compare the intraocular pressure (IOP)-lowering efficacy and safety of travoprost 0.004%/timolol 0.5% ophthalmic solution (Trav/Tim) to latanoprost 0.005%/timolol 0.5% ophthalmic solution (Lat/Tim), dosed once daily in the morning, in patients with open-angle glaucoma (OAG) or ocular hypertension (OH).*

METHODS. *This was a randomized, double-masked, multicenter, parallel group, active-controlled study conducted at 41 sites. At the eligibility visit the patients were randomized (1:1) to the assigned masked medication if they met inclusion/exclusion criteria, and the mean IOP values in the eligible eyes were ≥24 mmHg at 9 AM and ≥21 mmHg at 11 AM and 4 PM. Patients were excluded if the mean IOP in either eye was >36 mmHg. Patients were instructed to administer the assigned medication each morning at 9 AM. During the treatment phase of the study, IOP was measured at 9 AM at week 2, week 6, month 3, and month 9. At the month 6 and month 12 visits, IOP was measured at 9 AM, 11 AM, and 4 PM. Statistical methods included a repeated measures analysis of variance (ANOVA); to test for noninferiority, a 95% confidence interval for the treatment group difference was constructed based on the ANOVA results for each time point at month 12.*

RESULTS. *Patients (n=408) with OAG or OH were enrolled at 41 sites. One patient withdrew prior to receiving medication so 207 in the Trav/Tim group and 200 in the Lat/Tim group were evaluable for safety. Baseline demographic characteristics as well as IOP values showed no statistical differences between the two groups. Trav/Tim provided lower mean IOP values than Lat/Tim that were statistically significant at the week 2 9 AM (p=0.0081), month 6 9 AM (p=0.0056), and month 6 11 AM (p=0.0128) time points and at 9 AM time point pooled across all visits (p=0.0235) when mean IOP was 0.6 mmHg lower in the Trav/Tim group. Treatment-related adverse events were mild in both groups. Although hyperemia was reported from a higher percentage of patients in Trav/Tim group, differences in average hyperemia scores between the two groups were not considered clinically relevant.*

CONCLUSIONS. *Travoprost 0.004%/timolol 0.5% ophthalmic solution produced mean IOP levels that are statistically noninferior to latanoprost 0.005%/timolol 0.5% ophthalmic solution. Furthermore, at 9:00 AM, 24 hours after dosing, IOP was statistically lower for travoprost 0.004%/timolol 0.5% pooled across all visits. Travoprost 0.004%/timolol 0.5% fixed combination ophthalmic solution is an effective treatment for reducing IOP and it is safe and well-tolerated in patients with OAG or OH. (Eur J Ophthalmol 2007; 17: 183-90)*

KEY WORDS. *Travoprost, Timolol, Latanoprost, Glaucoma, Intraocular pressure*

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INTRODUCTION

The prostaglandin class of intraocular pressure (IOP)-lowering medications offers unrivaled efficacy and safety in patients with glaucoma or ocular hypertension. Beta blockers, long the mainstay of glaucoma therapy, are a common adjunctive choice for patients inadequately controlled on prostaglandin monotherapy. To maximize convenience and compliance with therapy, fixed combinations containing drugs of these two classes have been developed.

Latanoprost 0.005%/timolol 0.5% fixed combination (Xalacom®, Pfizer Inc.) is available in several international markets. Travoprost 0.004%/timolol 0.5% fixed combination (Alcon Laboratories, Inc., Fort Worth, TX, USA) has also been developed for the lowering of IOP. The safety profiles of travoprost and latanoprost are similar (1, 2). Travoprost has been shown to have a greater IOP-lowering effect 20 and 24 hours after dosing (2, 3), which may be related to its high affinity and full agonist efficacy at the FP receptor (4, 5). The goal of this clinical trial was to compare the IOP-lowering efficacy and safety of once-daily travoprost 0.004%/timolol 0.5% ophthalmic solution to once-daily latanoprost 0.005%/timolol 0.5% ophthalmic solution in patients with open-angle glaucoma or ocular hypertension.

MATERIALS AND METHODS

Patient enrollment and randomization

This was a prospective, randomized, double-masked, multicenter, parallel-group, active-controlled study. The protocol was approved by the appropriate independent ethics committees at all of the 41 participating study centers, and all patients provided written informed consent to participate.

Potential patients attended a screening visit, at which time informed consent was obtained, demographics and medical history were recorded, and the medical record was reviewed for eligibility. Patients with open-angle glaucoma (including pseudoexfoliation or pigment dispersion) or ocular hypertension were eligible to participate if they had received treatment with at least one IOP-lowering medication and were either inadequately responsive or intolerant to the medication. Such patients were eligible if it was deemed safe

TABLE I - BASELINE DEMOGRAPHICS BY TREATMENT GROUP

	Total	Trav/Tim	Lat/Tim	p value*
Mean age, yr		64.8	64.9	0.9655
Total, n (%)	332 (100.0)	168 (50.6)	164 (49.4)	
Sex				
Male	136 (41.0)	64 (38.1)	72 (43.9)	0.2820
Female	196 (59.0)	104 (61.9)	92 (56.1)	
Ethnicity				
White	304 (91.6)	152 (90.5)	152 (92.7)	0.6893
Asian	27 (8.1)	15 (8.9)	12 (7.3)	
Other	1 (0.3)	1 (0.6)	0 (0.0)	
Iris color				
Brown	161 (48.5)	79 (47.0)	82 (50.0)	0.9465
Hazel	23 (6.9)	12 (7.1)	11 (6.7)	
Green	22 (6.6)	11 (6.5)	11 (6.7)	
Blue	89 (26.8)	45 (26.8)	44 (26.8)	
Grey	37 (11.1)	21 (12.5)	16 (9.8)	
Diagnosis				
Ocular hypertension	64 (19.3)	34 (20.2)	30 (18.3)	0.5590
Primary open-angle glaucoma	233 (70.2)	115 (68.5)	118 (72.0)	
Pigmentary glaucoma	8 (2.4)	6 (3.6)	2 (1.2)	
Pseudoexfoliation glaucoma	27 (8.1)	13 (7.7)	14 (8.5)	

*p value from chi-square or Fisher exact test. Trav/Tim = Travoprost 0.004%/timolol 0.5%; Lat/Tim = Latanoprost 0.005%/timolol 0.5%

to discontinue all IOP-lowering therapy for a variable washout period of 5 to 28 days (5 days for miotics and topical or oral carbonic anhydrase inhibitors, 14 days for alpha- and alpha-beta agonists, and 28 days for beta blockers and prostaglandin analogues; fixed combination drugs were washed out according to the component with the longest washout period). In addition, contact lens wearers were required to instill study medications at least 15 minutes before inserting lenses.

Exclusion criteria included any form of glaucoma other than open-angle glaucoma (including pseudoexfoliation and pigment dispersion) or ocular hypertension; visual acuity worse than 0.6 logMAR in either eye, or an angle judged less than grade 2 on gonioscopy, cup-disc ratio greater than 0.8 in either eye, advanced visual field loss in either eye; any history of chronic or severe inflammatory eye disease, ocular infection or inflammation or ocular laser surgery within the past 3 months, ocular trauma or intraocular surgery within the past 6 months; any clinically relevant or progressive retinal disease; any ocular abnormalities precluding reliable applanation tonometry; or any ocular or systemic condition for which therapy with a beta blocker or prostaglandin analogue would be contraindicated (such as severe dry eye, macular edema, or pulmonary, cardiovascular, renal, or hepatic disease). In addition, patients who began therapy within 30 days of enrollment with a systemic medication that might affect IOP or any investigational medication were deemed ineligible. Patients requiring therapy with systemic glucocorticoids at any time during the trial were also excluded. Furthermore, breastfeeding or pregnant women, women who intended to become pregnant, and women who were not using a reliable form of birth control were excluded.

Successfully screened patients discontinued all IOP-lowering therapy for the required washout period before attending an eligibility visit. At this visit, IOP was measured in both eyes at 9 AM, 11 AM, and 4 PM. To be eligible for randomization, patients were required to have an IOP of ≥24 mmHg at 9 AM and ≥21 at 11 AM and 4 PM in at least one eye (and the same eye at all three time points), with neither eye having an IOP > 36 mmHg at any time point.

Patients meeting all of these criteria were randomized in a 1:1 ratio to therapy with either travoprost 0.004%/timolol 0.5% (the Trav/Tim group) or latanoprost 0.005%/timolol 0.5% (the Lat/Tim group), each in fixed combination and dosed once daily at 9 AM in both eyes, whether or not both met eligibility requirements (unless a contraindication to treatment existed in the nonqualifying eye, in which case only the qualifying eye was treated). To ensure proper masking, both study medications were supplied in identical oval, opaque bottles. Randomization was achieved by enrolling qualified patients in a sequential manner by patient number, beginning with the first number assigned to each site; this numerical sequence of patient numbers contained a built-in computer-generated randomization such that patients were randomly assigned to treatment groups in accordance with the planned assignment ratio.

Schedule of evaluations

For analysis, IOP for each eye at each time point was defined as the mean of two measurements if within 4 mmHg of one another. If the two measurements differed by more than 4 mmHg, a third measurement was taken; in this case, the IOP for analysis was calculated as mean of the two measurements closest to each other, or the mean of all three if equidistant from each other. Only one eye per patient was selected for analysis. For patients treated in both eyes, this was the eye with the higher IOP at the eligibility visit at 9 AM, or if the two eyes were equal, at 11 AM, or if equal, at 4 PM, or if equal, then the right eye.

After randomization, scheduled evaluations took place at weeks 2 and 6, and at months 3, 6, 9, and 12 after beginning study medication. Specific assessments at each of these visits occurred as follows: IOP and conjunctival hyperemia were assessed at 9 AM on all scheduled study visits, at 11 AM and at 4 PM on month 6 and month 12 visits. IOP was measured with Goldmann applanation tonometry, and two measurements were taken (three if the first two differed by more than 4 mmHg) at each time point on each visit. Current health status and medication usage were queried and recorded at all visits and all time points, including at 11 AM on the week 2 visit. Visual acuity was measured (best-corrected, logMAR scale), biomicroscopy was performed, and ocular photographs (open and closed eye) were taken at the beginning of each visit. Resting blood pressure and pulse were measured at all visits and time points, except the 4 PM time points on

the eligibility and month 6 and 12 visits. Gonioscopy, automated perimetry (most sites), and a dilated fundus examination were performed both at screening and at the month 12 visit. Adverse events were solicited at all visits and time points beginning immediately after first installation of the study medication.

Statistical analysis

The primary statistical objective of this study was to demonstrate that the IOP-lowering efficacy of Trav/Tim was noninferior to Lat/Tim. The primary efficacy parameter was the assessment of mean IOP. Primary inference for noninferiority was based upon the 9 AM, 11 AM, and 4 PM mean IOP at month 12.

All patients who received study medication were included in the safety analysis. All patients who completed the study with no protocol violations were included in the per-protocol analysis which was used for the efficacy results in this report.

Hypothesis testing was performed using repeated measures analysis of variance. For the test of noninferiority, a 95% confidence interval for the treatment group difference was constructed based on the analysis of variance at each time point at month 12. Primary inference for the test of noninferiority was based on the per-protocol data set.

Based on an assumed standard deviation for IOP of 3.5 mmHg and a 5% chance of a Type I error, a sample size of 142 evaluable patients in each treatment group provided a 90% coverage probability that a 95% two-sided confidence interval would fall within ±1.5 mmHg. Since only one side of this tolerance region is relevant for a noninferiority comparison, for differences based on mean IOP in the Trav/Tim group minus mean IOP in the Lat/Tim group, the upper 95% confidence limit was compared to +1.5 mmHg (2). In addition, descriptive statistics were calculated for IOP, IOP change from baseline, and IOP percent change from baseline. Mean IOP change from baseline was also estimated using a repeated measures analysis of variance.

RESULTS

Overall, 408 patients were enrolled and randomized to one of the two treatment groups. One patient withdrew before receiving any study medication, leaving 407 patients available for the safety analysis Trav/Tim (n = 207) or Lat/Tim (n = 200). A total of 10 patients discontinued the study before the collection of any on-treatment data. A total of 76 patients (the 10 who had no on-therapy data and 66 with protocol violations) were excluded from the per-protocol data set. The protocol violation most frequently resulting in patient exclusion was nonqualifying IOP, or violation of IOP measurements.

Baseline demographic information for the 332 patients included in the per-protocol analysis is given in Table I. Patients were typically women (59%), white (92%) or Asian (8%). They averaged 64.8 years in age and were diagnosed with open-angle glaucoma (70.2%), ocular hypertension (19.3%), pigmentary glaucoma (2.4%), or pseudoexfoliation glaucoma (8.1%). There were no statistically significant differences in baseline characteristics between the two treatment groups.

TABLE II - MEAN IOP (in mmHg) COMPARISON OF TRAVOPROST 0.004%/TIMOLOL 0.5% AND LATANOPROST 0.005%/TIMOLOL 0.5% DOSED ONCE DAILY AT 9 AM

	Baseline (mmHg)			Combined (mmHg)		
Treatment	**9 am**	**11 am**	**4 pm**	**9 am**	**11 am**	**4 pm**
Trav 0.004%/Tim 0.5%						
Mean	27.0	25.8	24.6	17.1	16.5	16.4
No.	168	168	168	167	153	153
Lat 0.005%/Tim 0.5%						
Mean	27.3	26.1	25.2	17.7	17.1	16.7
No.	164	164	164	163	153	152
P Value	0.5437	0.4551	0.0772	0.0235	0.1100	0.3657

Combined data were pooled from the week 2, week 6, month 3, month 9, and month 12 visits. IOP = Intraocular pressure

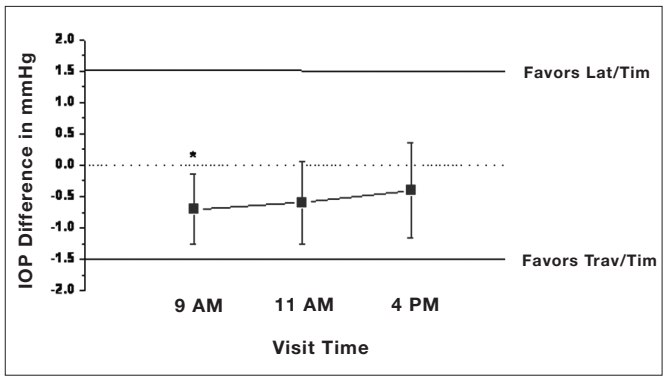

Fig. 1 - *Mean intraocular pressure difference averaged across all time points between travoprost 0.004%/timolol 0.5% and latanoprost 0.005%/timolol 0.5% dosed once daily at 9 am. *p<0.05.*

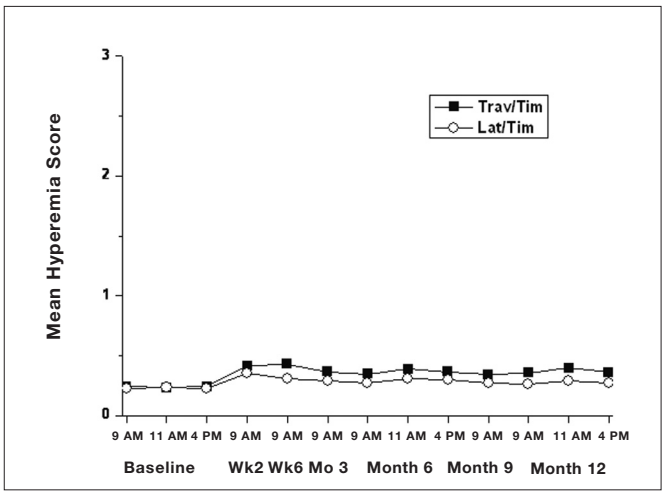

Fig. 2 - *Summary of mean hyperemia scores for the overall safety population from physician assessments for patients on travoprost/004%/timolol 0.5% or latanoprost 0.005%/timolol 0.5% therapy. Scale: 0 = none, 1 = mild, 2 = moderate, 3 = severe.*

Intraocular pressure

IOP at baseline and on study treatment at all visits and time points is given in Table II. Trav/Tim and Lat/Tim provided significant reductions in IOP from baseline at all time points ($p<0.001$). Trav/Tim provided 0.6 mm Hg lower mean IOP than Lat/Tim at 9 AM ($p=0.0235$). Trav/Tim dosed once-daily in the morning produced reductions from baseline in IOP ranging from approximately 8 to 10 mmHg, and representing a relative reduction of up to 38% from baseline. Lat/Tim produced reduction from baseline in IOP ranging from about 8 to 10 mmHg, which represented a relative reduction of up to 37%. IOP levels of less than 18 mmHg were achieved in 51% or more of patients in the Trav/Tim treatment group and at least 41% of patients in the Lat/Tim group. Differences in mean IOP favored travoprost 0.004%/timolol 0.5% over latanoprost 0.005%/timolol 0.5% at the week 2 9 AM ($p=0.0081$), month 6 9 AM ($p=0.0056$), and month 6 11 AM ($p=0.0128$) time points. The treatment group differences favoring travoprost 0.004%/timolol 0.5% ranged from 0.3 to 1.0 mmHg. At 9 AM Trav/Tim produced statistically lower mean IOP than Lat/Tim ($p=0.0235$) when pooled across all visits (Fig. 1). After adjusting for baseline IOP, the statistically significant differences observed in the original analysis remained significant.

Safety

Adverse events in the overall study safety population were predominantly nonserious, generally mild to moderate in intensity, and generally did not result in discontinuation from the study. Thirteen patients in the Trav/Tim group and 10 patients in the Lat/Tim group discontinued participation in the study due to adverse events (difference not significant, $p=0.5760$).

Ocular adverse events were generally mild. Treatment-related ocular adverse events occurring in the Trav/Tim group at an incidence of greater than 1% were hyperemia (15%), ocular pruritus (6.8%), ocular discomfort (4.3%), eyelash changes (2.4%), ocular dryness (1.9%), and ocular pain (1.4%). In the Lat/Tim group, ocular discomfort (3.5%) and foreign body sensation (3.5%) were the most frequent treatment-related ocular adverse events, followed by hyperemia (2.5%) and pruritus (2%) (all had an incidence >1%). Mean hyperemia scores were generally similar, although differences were statistically significant ($p<0.05$) at 2 of 10 study visits. Overall, mean scores were in the trace to mild range (0.2 to 0.4 on a scale of 0, none to 3, severe) and the differences between groups were not considered clinically relevant (Fig. 2).

Systemic adverse events possibly related to treatment in the Trav/Tim group included two patients with skin discoloration, and one patient each with allergy, headache, hypertension, dizziness, asthma, worsened cough, and systemic dyspnea. Treatment-related adverse events in the Lat/Tim group included one patient each with headache, dry mouth, tongue edema, vertigo, herpes simplex, and tinnitus. Two patients died during the

study, and both deaths were assessed as unrelated to study drug. These included one patient in the Trav/Tim group who had a myocardial infarct, and one patient in the Lat/Tim group who had peritonitis and cholecystitis.

DISCUSSION

Travoprost 0.004%/timolol 0.5% ophthalmic solution (Trav/Tim) produces statistically significant ($p<0.001$ at all time points) and clinically relevant IOP reductions when dosed once daily in the morning. Previous studies have demonstrated that the fixed combination provides superior IOP reduction compared to monotherapy with either component (6), and provides similar IOP reduction to concomitant dosing with travoprost and timolol dosed separately (7, 8). The current study confirms these prior reports, demonstrating IOP reductions on the order of 8 to 10 mmHg with once-daily dosing, representing relative IOP reductions of 30% to 38% from an untreated baseline. The values for mean IOP for patients on Lat/Tim therapy agree with previous studies. Diestelhorst et al, for example, conducted a crossover clinical trial in which patients who were currently on the unfixed combination of latanoprost 0.005% and timolol 0.5% were randomized to either continue treatment for 6 weeks or to initiate treatment with the fixed combination of Lat/Tim (9). After the patients were crossed over, the average diurnal IOP was 17.2 and 16.9 mmHg for the fixed combination therapy at weeks 6 and 12, respectively. This study did not include a washout period. Another study by Hamacher et al (10) evaluated patients who were switched from their current monotherapies or adjunctive therapies to Lat/Tim. There was no washout period in this study. Open- angle glaucoma patients who began with a mean baseline of 20.6 mmHg showed IOP reductions to 17.6 mmHg following Lat/Tim therapy. Both of these published studies with Lat/Tim reported IOPs similar to those observed in the current study (Tab. II). This study compared the IOP reduction of Trav/Tim and Lat/Tim. This was a multinational study conducted in countries where Lat/Tim is commercially available. Results of the study demonstrate that Trav/Tim produces mean IOP levels that are statistically noninferior to Lat/Tim. The predetermined noninferiority criterion (upper limit of the 95% confidence interval below 1.5 mmHg) was met at every study visit and time point. This included all three time points at the month 12 visit, which were the primary efficacy endpoints. Furthermore, Trav/Tim produced a statistically lower mean IOP than Lat/Tim at several time points (week 2 and month 6 at 9 AM and month 6 at 11 AM), including also the pooled data from the 9 AM time points. The treatment group differences favoring Trav/Tim ranged from 0.3 to 1.0 mmHg. It is at the discretion of the ophthalmologists to consider whether differences of 0.3 to 1.0 mmHg in IOP lowering effectiveness are clinically significant. IOP is often highest in the morning. Drugs that excel at IOP reduction at this time of day offer the potential for improved diurnal control, which may reduce the risk of glaucomatous progression independently of mean IOP reduction (11, 12).

Travoprost 0.004%/timolol 0.5% was well tolerated by patients in this study. The nature of adverse events was similar to those reported for latanoprost 0.005%/timolol 0.5%, as were discontinuation rates for both drugs. Side effects were generally ocular, and primarily attributable to the prostaglandin component of the combination. Although hyperemia was reported from a higher percentage of patients in Trav/Tim group, differences in average hyperemia scores between the two treatment groups were not considered clinically relevant. Siegel et al conducted a study in which physicians masked as to the therapy were not able to determine whether the patient was undergoing latanoprost 0.005% or travoprost 0.004% treatment (Siegel LI, Saroli TL, Jenkins JN, et al. Conjunctival hyperaemia with latanoprost 0.005% versus travoprost 0.004% in patients previously treated with latanoprost 0.005%. Presented at the European Association for Vision and Eye Research EVER meeting; September 2005; Vilamoura, Portugal). A recent study by Chang showed that 87% of patients responded that hyperemia would not cause them to discontinue their medication (Chang EJ. Patient perspectives on hyperaemia. Presented at The American Society of Cataract and Refractive Surgery; April 2005; Washington, DC). Moreover, 92% of patients wanted the most effective IOP-lowering agent, despite the possibility of hyperemia. These data demonstrated that patients who understand the severity of their disease and the importance of IOP lowering are willing to tolerate cosmetic side effects in order to receive the most effective therapy.

Many patients with glaucoma require more than one

topical IOP-lowering medication to achieve adequate control of IOP (13). Fixed combinations, such as travoprost 0.004%/timolol 0.5% ophthalmic solution, offer numerous benefits to patients with glaucoma on multidrug regimens. Two complementary IOP-lowering agents in one bottle offer convenience of dosing, which may improve compliance (14). A single prescription may have an economic benefit for the patients as well as the healthcare system. Delivering two medications in a single drop also minimizes the washout effect, in which two medications are administered too closely together in time, permitting the second drop to wash away the first drop before maximal ocular penetration has occurred (15). Also, two medications in one drop reduces total ocular exposure to preservatives in the formulation, which may cause chronic conjunctival inflammation (16) and reduce the success of subsequent filtering surgery (17).

This was a multinational study conducted in countries where latanoprost 0.005%/timolol 0.5% ophthalmic solution has already achieved regulatory approval and is available in the marketplace. The results of the study demonstrate that travoprost 0.004%/timolol 0.5% ophthalmic solution produces mean IOP levels that are statistically noninferior to latanoprost 0.005%/timolol 0.5% ophthalmic solution. The predetermined noninferiority criterion (upper limit of the 95% confidence interval below 1.5 mmHg) was met at every study visit and time point. This included all three time points at the month 12 visit, which were the primary efficacy endpoints.

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APPENDIX

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