

Trends-in-Medicine

February 2007

by Lynne Peterson

SUMMARY

- Glaucoma. Sales of prostaglandins have flattened. Interest is high in neuroprotective agents, but as adjunctive therapy, not monotherapy, and insurance coverage and price will dictate use.
- Dry eye. Use of Allergan's Restasis is low and unlikely to increase much unless the price is lowered, though more samples for optometrists and a continuation of direct-to-consumer advertising may help.
- Contact lenses. CooperVision's silicone hydrogel lens is not expected to be launched until perhaps September 2007, and Johnson & Johnson/Vistakon appears to be picking up quite a bit of business in the wake of Novartis/Ciba Vision's recall of some O₂Optix lenses.
- Contact lens solutions. Corneal staining is getting increasing attention, and it appears to be due to a mis-match of lenses and solutions, with the most problematic Bausch & Lomb's ReNu and the least Alcon's Opti-Free, but this is not confirmed yet.
- Multifocal IOLs. Interest is increasing, especially for cataract patients but also for refractive lens exchange.
- Refractive surgery. The market is maturing and flattening, with price, contact lens improvements, patient fears, and the economy all playing a role. In addition, many patients especially presbyopes want more than LASIK can deliver, but presbyopic LASIK is not yet ready for prime time.

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Trends-in-Medicine

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EYE CARE UPDATE

To check on trends in the eye care field, 129 optometrists from 14 states and Canada were interviewed at the Broward County Optometric Association's Gold Coast Educational Retreat in Ft. Lauderdale on January 20 and 21, 2007. They offered opinions and outlooks on medications for glaucoma, dry eye, and ocular allergies as well as contact lenses, contact lens solutions, back-of-the-eye products, multifocal intraocular lenses (IOLs), and refractive surgery.

GLAUCOMA

Over the next 6-12 months, doctors predicted that their prescriptions for prostaglandin analogs – Alcon's Travatan (travoprost), Allergan's Lumigan (bimatoprost), and Pfizer's Xalatan (latanoprost) – will be flat. Most (73%) do not expect laser treatments for glaucoma to have any impact on prostaglandin prescriptions.

Prostaglandin Usage Outlook Among Glaucoma Patients

Glaucoma medication	% of glaucoma patients taking it now	% of glaucoma patients who will be taking it in 6-12 months
Alcon's Travatan (travoprost)	21%	22%
Allergan's Lumigan (bimatoprost)	20%	25%
Pfizer's Xalatan (latanoprost)	49%	49%
Other	10%	4%

Among the other interesting findings on glaucoma were:

- These doctors were not aware of any significant drugs in development to treat glaucoma.
- In June 2006, Allergan got a first-line indication for Lumigan, but most doctors (73%) said that will **not** boost their use of that drug.
- If the FDA approved Allergan's Combigan (the fixed dose combination of brimonidine + timolol), it would not expand the number of patients on a glaucoma medication, but nearly half (41%) of doctors would switch to it from another drug, most often, from Merck's Cosopt (dorzolamide HCl + timolol maleate) and, to a lesser extent, from Allergan's Alphagan (brimonidine) and Pfizer's Xalatan.

Neuroprotection

Forest Laboratories Namenda (memantine) is approved to treat for Alzheimer's Disease, and Allergan, which has the rights to memantine for ophthalmic uses, is

currently testing it in a Phase III trial as a neuroprotectant for glaucoma. At the American Academy of Ophthalmology meeting in November 2006, ophthalmologists were optimistic about the outlook for this trial, and retina surgeons were predicting that they would give it off-label to "all" of their age-related macular degeneration (AMD) patients if the trial is positive. Only one of these optometrists has any patients currently getting Namenda off-label for neuroprotection in glaucoma or AMD.

Nearly two-thirds of optometrists (63%) believe memantine will prove an effective neuroprotectant in glaucoma. An expert predicted it may show a small effect, but cautioned that the drug's side effects may limit its usefulness to only the most severe glaucoma patients, "Memantine may well work, but I'm not sure it will ultimately be the drug of choice. It may or may not be powerful enough, but a significant number of people will find the side effects outweigh the benefit. It may be used for a small percentage of glaucoma patients with very, very fast, progressive, serious disease – the ones who go blind. In those patients it may well be worth the risk of side effects...There are an awful lot of promising candidates for neuroprotection. The problem is everyone is struggling to find one that really works in humans."

Optometrists were not sure whether or not the mechanism action of memantine is glutamate reuptake inhibition that prevents retinal ganglion cell death. Even experts are not sure. As one explained, "Memantine is an NMDA antagonist, but we don't know that that prevents retinal ganglion cell death. That is the assumption, but it has not been proven yet. We know retinal ganglion cells die, and that glutamate usually plays a role in that cascade, but whether blocking glutamate will help with glaucoma is unknown...We still don't know if it will target retinal ganglion cells well enough. With the eye, it is all about targeting."

The primary endpoint in the 4-year memantine glaucoma trial is optical field measurement, not intraocular pressure (IOP) lowering. Doctors were almost evenly divided as to whether or not this is long enough to be definitive. An expert was critical of the length of the trial, "It could be long enough if they selected the patients right, but that would be a more difficult study to do."

If the trial is positive, the optometrists who were questioned predicted that an average of 11% of their glaucoma patients would get Forest's Namenda (memantine) off-label until Allergan's memantine is approved. If the FDA approves memantine as a neuroprotectant for glaucoma, doctors predicted that:

- > 17% of their glaucoma patients would be on it six months after approval.
- It would be used primarily as adjunctive therapy, not monotherapy, in low IOP patients.
- Patients would probably take it "forever."

- Managed care coverage will be important, but only 15% believe managed care will cover it, while half (52%) doubted managed care companies would cover it, and 33% were unsure. Even when it is covered, several sources pointed out, the insurance co-pay is too steep for many patients.
- Patient demand for a drug like memantine is hard to measure. Half the sources believe it will be strong, and the other half think demand will be weak.
- The actual usage of memantine for glaucoma is expected to be determined by:
 - 36% data on neuroprotection
 - 22% price
 - 19% direct-to-consumer (DTC) advertising
 - 11% oral administration (vs. eye drops such as the prostaglandins)
 - 6% efficacy
 - 3% compliance
 - 3% other

The main reason doctors cited for combining memantine with other theoretical neuroprotectants (e.g., Alphagan) would be to improve neuroprotection – to perhaps get a synergistic effect, or as a "shotgun approach to try to take advantage of possible different mechanisms."

A key question with respect to the outlook for memantine is whether it will be used for normotensive (low tension) glaucoma patients. Normotensive glaucoma accounts for ~30% of all glaucoma in the U.S. It is not associated with elevated intraocular pressure (IOP); normotensive glaucoma patients have normal IOP but some level of optic nerve damage.

Optometrists reported that fewer of their patients had normotensive glaucoma than this national average, estimating that only 10% of their glaucoma patients are normotensives. Most often they treat them with a prostaglandin (81%), but also with Alphagan (11%) and/or a beta blocker. However, slightly more than half the sources (55%) said they would prescribe or recommend a prescription product as a glaucoma neuroprotective if it was priced at a premium to (higher than) the prostaglandins. Since memantine is expected to be used as adjunctive therapy, they think it is unlikely memantine will cannibalize Alphagan use.

Compliance with glaucoma medications has been a problem. Experts have estimated that only about half of glaucoma patients in the U.S. have been diagnosed, and even when patients are diagnosed and started on glaucoma medications, many are not compliant with the regimen or drop therapy altogether. More than half the doctors questioned (59%) believe patients will be more compliant with an oral agent than with eye drops.

DRY EYE

Few of these optometrists' dry eye patients (11% on average) currently take Allergan's Restasis (cyclosporine A), and that is likely to increase very little over the next six months – to just an average of 14%. The problem is not requirements by managed care companies for prior authorization for use of Restasis, but cost.

Allergan's direct-to-consumer (DTC) advertising campaign for Restasis has caused patients to ask about Restasis more, and it has caused a few doctors to prescribe it more. Most doctors think the DTC program is helpful and positive. Among the positive comments were:

- "It's a good thing."
- "Any eye care advertising is good."
- "It increases patient awareness."
- "It's great. It gets people to ask and be more informed."
- "It's good, so patients won't be amazed at the cost and the (need for) long usage."
- "It's okay, but it is somewhat misleading."
- "It makes patients more open to trying Restasis."

A few doctors also had some negative comments about the Restasis DTC advertising:

- "I disapprove of direct-to-patient advertising."
- "DTC sucks, and Restasis doesn't work."
- "When patients find out the cost, they don't ask further questions."
- "There is not enough information for the patient."

Sources suggested that the main things Allergan needs to do to boost use of Restasis are to lower the price and increase samples for optometrists. Other suggestions included: changing the formula to reduce the "high rate" of adverse reactions, do more educating of prescribers, find a way to make it work faster, and get it covered by more insurance plans.

Among the other agents in development to treat dry eye are:

- Generic cyclosporines.
- Inspire's diquafosol. A source said, "It will be tough to get FDA approval on this, based on the clinical data."
- Novartis's rebamipide. An expert called this "promising."
- Novartis's Elidel (pimecrolimus).
- Alcon's 15(S)-HETE.
- Santen. The company has some agent in development, but sources didn't know anything about it.

OCULAR ALLERGIES

Allergy Medication Use

Allergy medication	Patient use
Alcon's Patanol (olopatadine HCl 0.1% and 0.2%)	65.8%
Novartis's Zaditor (ketotifen fumarate 0.025%)	8.5%
Allergan/Inspire's Elestat (epinastine HCl 0.05%)	8.1%
B&L's Alrex (loteprednol etabonate 0.2%)	6.1%
B&L's Optivar (azelastine HCl 0.05%)	5.7%
Novartis's Livostin (levocabastine 0.05%)	3%
Allergan's Acular LS (ketorolac tromethamine 0.4%)	1.8%
Alcon's Emadine (emedastine difumarate 0.05%)	1%

Inspire's Elestat was approved by the FDA in 2003 for the prevention of itching associated with allergic conjunctivitis. Nearly half of these doctors prescribe it. The key competitor for Elestat is Alcon's Patanol. Nearly two-thirds of these doctors expect their use of Elestat to *decrease* over the next six months, even though they generally had good comments about Elestat:

- "It works well at Day 9."
- "It is very effective and quick acting."
- "I love Elestat. Patients love it as well."
- "I just heard about it last week."
- "It is not a big enough brand."
- "The response is variable from patient to patient."
- "It burns too much."
- "It is not as effective (as Patanol)."
- "I think both Patanol and Elestat are good, but Elestat is better for allergic DES (dry eye syndrome)."

CONTACT LENSES

COOPERVISION. Over the past 6-9 months, more than twothirds of these doctors said they either have had no or limited contact with a CooperVision sales rep, and many described their interaction with their CooperVision sales rep as bad.

A source said the company has given sales reps no indication about when the company's silicone hydrogel lenses will be launched, and she does not expect them before at least 2Q07. A large distributor said he doesn't expect the launch until September 2007.

NOVARTIS/CIBA VISION. On January 17, 2007, Ciba Vision recalled select lots of its O₂Optix silicone hydrogel lenses. A Ciba official said: "(We) identified that some lenses in these lots may fall below our standard for ion permeability, a material characteristic that correlates with lens movement on the eye. Reduced ion permeability in O₂Optix (lotrafilcon B) lenses may lead to reduced lens movement, symptoms of discomfort, and/or foreign body irritation...The potential

medical safety risk to consumers posed by lenses with reduced ion permeability includes discomfort, foreign body irritation, and superficial localized corneal staining. The possibility of occurrence of these findings is moderate. As with any staining of the corneal tissue, the risk of corneal infection is somewhat increased, although the probability is remote."

Only about half of these doctors were aware of the recall, and most expect the lenses to be available again soon: 29% estimated they would be available again within a month, 43% estimated 4-6 weeks, and 28% thought it would take more than two months before broad availability returned.

Prior to the recall, an average of 21% of these doctors' patients were fitted with any Ciba Vision lens, and doctors predicted this would drop to 17% of their total contact lens fits in six months. Most doctors are switching patients to Johnson & Johnson/Vistakon's Acuvue lenses, but others plan to switch to a variety of other lenses.

Switching Choices for Ciba Vision O2Optix Lenses

Lens	Percent of doctors switching from O ₂ Optix to this
Johnson & Johnson/Vistakon's Acuvue, Acuvue Oasys, or Acuvue Advance	70%
Novartis/Ciba Vision's Night & Day	12%
Bausch & Lomb's PureVision	6%
CooperVision's Proclear	2%
Other	10%

Incentives. According to these doctors, most of the contact lens manufacturers are offering some type of incentive, generally rebates.

Incentive Programs

Company	Type of Incentive
Bausch & Lomb	\$30-\$60 rebates, especially on PureVision, generally to doctors, but sometimes for patients.
Benz Research & Development (Extreme H ₂ O)	Buy 2-3 boxes and get 1 free. Patient discount coupons.
Ciba Vision	Most often rebates up to \$100 with a 2 box order of Night & Day. Some rebates on O ₂ Optix.
CooperVision	Rebates of up to \$80, coupons.
Johnson & Johnson/Vistakon	\$30-\$50 rebates on all products. Discounts on bulk orders.
Ocular Science	Patient rebates

CONTACT LENS SOLUTIONS

Bausch & Lomb withdrew its ReNu MoistureLoc contact lens solution from the market last year after outbreaks of *Fusarium* keratitis. Since then, many reduced or totally stopped use of ReNu solutions, often recommending another brand, and a few increased patient education efforts. Sources estimated that, on average, 58% of their ReNu patients ultimately stopped using ReNu altogether, but an average of 27% resumed using it after the furor over *Fusarium* keratitis died down.

The contact lens solution these doctors most often recommend to patients is Alcon's Opti-Free, and over the next 6-12 months that is the brand expected to see the largest increase in use, with ReNu use decreasing substantially, even from current low levels. There are "rumblings" that Johnson & Johnson plans to enter the solution business, but sources had no concrete information on this, though they had heard the rumors.

B&L was not the only company with a contact lens recall last year. In November 2006 Advanced Medical Optics (AMO) recalled 18 lots (nearly 200,000 packages) of 12-ounce Complete MoisturePlus multipurpose contact lens solution and Complete MoisturePlus Active Packs due to possible bacterial contamination. AMO blamed production-line problems at a manufacturing plant in China that supplied both Japan and the U.S. for the problem. However, more than half the doctors (55%) had little or no concern about this recall, with 11% expressing a high level of concern, and 34% moderately concerned.

Corneal staining

Different brands of contact lens solution have different rates of corneal staining, most of these optometrists (72%) believe. Almost half of these doctors (45%) believe that ReNu has the highest rate of corneal staining. Overwhelmingly, sources said they believe that the different preservatives used in solutions from Alcon, AMO, and B&L have some mechanism that causes different rates of staining among these products. Most (61%) do not believe that corneal staining has become a bigger issue since the *Fusarium* keratitis issues with ReNu MoistureLoc last year, but a doctor who disagreed said, "It has become a bigger issue with me, and I would bet with the FDA as well."

The *potential* negative side effects from corneal staining are primarily blurred vision, discomfort, irritation, infection, and keratitis. But doctors also pointed out that corneal staining

Contact Lens Solution Preferences

Solution	Most frequently recommended now	Use to <i>increase</i> over the next 6-12 months	Use to decrease over the next 6-12 months	Preference for new patient starts
Bausch & Lomb's ReNu	5%	3%	78%	9%
Alcon's Opti-Free	69%	58%	3%	61%
Advanced Medical Optics' Complete	18%	18%	16%	25%
Novartis/Ciba Vision's Clear Care	5%	18%	0	0
Other/none	3%	3%	3%	5%

can compromise corneas, mildly decrease vision, and cause dry eye, edema, and even corneal ulcers. It can also lower lens wearing time.

Doctors were divided on what is *mostly* to blame for corneal staining:

- 37% blamed particular lenses.
- 24% blamed the contact lens solution.
- 11% blamed silicone hydrogel lenses specifically. Doctors estimated that 36% of patients with silicone hydrogel lenses sleep in them, on average for 8 nights in a row, and doctors were divided as to whether sleeping in silicone hydrogel lenses is part of the problem.
- 13% said the problem is due to a combination of solution and lens.
- 15% cited other causes, such as dehydration, dry eye, lack of patient compliance, contact lens over wear, and poor patient hygiene.

Asked what the various manufacturers have told them about corneal staining, half of these sources said they had been told nothing at all. Several said Alcon claimed its solution causes less corneal staining, but others said all the companies are making the same claim. A doctor said, "They all say everyone else's product causes corneal staining." Another commented, "Each of them has its own spin on it." A third said, "They all claim theirs is the best."

Experts said they believe that the problem is a mix-match of silicone hydrogel lenses and a contact lens solution. They agreed that mixing and matching contact lenses and solutions can affect corneal staining. That is, solution A may be more likely to cause corneal staining when used with X contact lenses, and solution B may be more likely to cause corneal staining when used with Y contact lenses. What is the optimal mix-match? Researchers are still trying to determine that. However, at this point, it appears that, of currently marketed solutions, Alcon's Opti-Free is the least likely to cause corneal staining with any contact lens, and Bausch & Lomb's ReNu is the most likely.

Gary Andrasko, OD, and Kelly Ryen, OD, have been researching this, and experts recommended their Contact Lens Research Services website (www.staininggrid.com). Dr. Andrasko has a private contact lens clinical research practice in Columbus OH. Dr. Ryen also is in private practice in central Ohio and acts as a co-investigator with Dr. Andrasko in many contact lens and lens solution studies. On the website is a Staining Grid that lists the average percentage of the cornea which was stained 2 hours after different combinations of contact lenses and solutions.

The role of silicone hydrogel lens in corneal staining remains controversial. One expert explained silicone hydrogels are not worse than other materials with respect to corneal staining, but another expert pointed out that an Australian researcher –

Fiona Stapleton, BSc, MSc, PhD, MCOptom, DCLP, FAAO, with Vision CRC in Sydney – is finding that the incidence of microbial infections secondary to contact lens wear, including silicone hydrogels, correlates most with the lens wearing schedule. He said, "Dr. Stapleton's work is significant because she has large numbers (of users) from all over Australia, and the work is being conducted in a very careful and well-planned way." However, he added that microbial infections secondary to contact lens wear are a multifactorial process.

Alcon is conducting a 200-patient, single-site, double-masked, randomized clinical trial (cross-over design) of contact lens/solution combinations. The primary endpoint is areas of corneal staining, and the severity of corneal staining is a secondary endpoint. The trial is expected to be completed in June 2007. Daily wear soft contact lens wearers are being observed at baseline, two, and four hours post-lens insertion.

Although this issue is getting increased attention, especially by experts, sources did not believe it would cause any significant shift in contact lens solution choices in the near future. Experts first need to agree on it, then the information needs to be disseminated to opinion leaders and physician educators, which sources did not think would happen quickly absent a critical event (e.g., FDA action), which no one was predicting or expecting. Alcon might get some marketing advantage, but any claims would have to be done carefully to avoid issues with the FDA, which, again, suggests this will not become a major market shifting issue quickly.

BACK-OF-THE-EYE PRODUCTS

Doctors were asked about their familiarity with – and predictions for – several back-of-the-eye products on the horizon. They ranked them this way:

- No. 1. Allergan's Posurdex. Most doctors thought dexamethasone delivered via Posurdex to treat retinal vein occlusion or diabetic macular edema is a good and promising idea. Few doctors were negative about it, but some thought it was too early to form an opinion. Comments included:
 - "It's a good idea for focal treatment."
 - "It's a fantastic concept."
 - "It's a good idea if it is effective."
 - "It's interesting, but I need to see some study results."
 - "It sounds great."
 - "Give it time. It will have some negative side effect that may outweigh its benefits."
 - "It's just another way to make money."
- No. 2. Bausch & Lomb's Retisert, a back-of-the-eye implant that slowly elutes fluocinolone acetonide.

- No. 3 (a distant 3). Alimera Sciences/Control Delivery Systems' Medidur, a tiny injectable device that delivers fluocinolone acetonide directly to the back of the eye. It is in clinical trials to treat diabetic macular edema (DME).
- No. 4 (no awareness whatsoever). Surmodics' I-Vation, an intravitreal drug-delivery implant that currently is being tested with triamcinolone acetonide in DME patients, but it is capable of delivering a variety of drugs on a sustained release basis for more than a year.

MULTIFOCAL IOLS

Patient interest in multifocal IOLs for cataracts or refractive lens exchange (RLE) is increasing, according to 69% of doctors. And more than half of them (58%) now recommend multifocal IOLs for patients considering these procedures, most often for cataract surgery, but also for RLE. Eighty-three sources predicted that their patients' use of multifocal IOLs for cataract surgery will increase over the next six months, but only 48% thought use for RLE would increase.

Multifocal IOL Preferences

Multifocal IOL	% choosing
Alcon's ReStor	37%
Advanced Medical Optics' ReZoom	20%
Neither	43%

REFRACTIVE SURGERY

There was no consensus on why LASIK procedure volume nationally has flattened and remained relatively flat for about a year. Among the reasons these doctors suggested were (listed in order of most commonly cited to least commonly cited):

The low hanging fruit has been picked.

- "Those who wanted it got it already."
- "This is a normal adopter curve. Within 10 years LASIK will become more common."
- "In the beginning, many patients had been waiting years for the treatment."
- "It's the result of a normal product cycle."
- "It's a maturing market, and there are an increased number of other options."
- "The initial boom is over."
- "The ideal age is 25-45, and the pent-up demand has been met."
- "The easy cases have been done."
- "The 'newness' factor has worn off."

Price.

- "It is still too expensive."
- "The cost of LASIK has not continued to drop."

Contact lenses have improved.

- "The advent of silicone hydrogel contact lenses, with their increased comfort, has had an impact."
- "There are better contact lens options better comfort, longer wear time. Happier contact lens patients are not converting to refractive surgery."
- "There are now better continuous wear contact lenses."

Patients want more than LASIK can deliver.

- "It is not the best way to correct presbyopia for someone on a computer all day."
- "It does not correct reading except monovision."
- "Older candidates (presbyopes) are having lens exchange procedures."
- "Many presbyopes want to be corrected for perfect distance and near vision."

Fear.

- "Not everyone is willing to risk it."
- "Many people are too scared, unqualified, or too poor."
- "Visual acuity doesn't remain stable four to six years out."
- "Patients are aware that complications occur a lot at budget centers, so they are a little more cautious."

The economy.

• "The economy is not as good as it was. People have less disposable income."

Advertising has decreased.

For LASIK procedure volume or their referrals for LASIK/refractive surgery to accelerate, doctors suggested:

- √ The price needs to come down.
- ✓ More national advertising would help, with an emphasis on the safety of the procedure. A doctor said, "People need proper education about the procedure. It needs to be treated less like a commodity." Another commented, "We need to educate the public about the safety and efficacy 'LASIK. It's for everyone now."
- ✓ **Get insurers to cover it.** A doctor said, "If the procedure gets covered by insurance, tons of people will do it."
- √ Develop new procedures/technology for presbyopes. A doctor said, "We need a presbyope solution other than monovision.
- √ Increase optometric co-management fees and improve optometry/ophthalmology relations.

Doctors were divided on the outlook for presbyopic LASIK. Half think current technology isn't good enough for them to recommend it to patients, but the others think it sounds promising.

LASIK pricing is generally remaining stable *in these doctors' markets*. Few doctors (26%) reported any increase in competition in their area for refractive surgery patients from new chains compared to this time last year. Doctors who have an LCA-Vision center near them said the marketing approaches they are seeing by LCA-Vision are *(in order of mention)*:

- Low prices.
- Advertising TV, newspaper, and, especially, radio of low price *plus* an emphasis on quality. Several doctors compared this advertising to car dealer-type ads.
- Coupons.
- Internet advertising.

Comments on Presbyopic LASIK

Positive	Negative
"It sounds promising."	"It is inferior monovision."
"It's a nice idea if it works better than multifocal soft contact lenses."	"It isn't smart."
"It's a good procedure if you screen for the proper patients."	"It's only monovision."
"I would broaden the patient base."	"It's a poor choice for presbyopia."
"I'm interested. That's why I and some of my patients haven't had LASIK."	"It requires a time-intensive explanation to the patient."
"I'm very interested. I have a lot of patients in this category."	"It is not the greatest option for my patients."
"I'm very interested, but it is still experimental."	"It's absurd."
"It must be better than multifocal contact lenses or I'm not interested."	"It doesn't work well."
"My interest level is high."	"I don't like the concept. It's useless."
"I'm not opposed, but I haven't seen any studies on success or patient satisfaction."	"I have no interest. Refractive implantable contact lenses are much better."
	"It's a real waste."

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