sure (IOP) patterns are not repeatable in the short term in healthy eyes. Although the authors carefully do not discourage the use of diurnal IOP monitoring, a cursory reading of this study may give the impression that such testing is not useful. Diurnal fluctuation in IOP has been implicated but not proven to be an independent risk factor for glaucoma progression.

I had never assumed that any given measurement, either sporadic or diurnal, is repeatable in either the short term or the long term but I still think diurnal IOP measurement offers valuable information in many clinical cases. The statistical results of this study do not negate the use of this test in any given eye. In my experience, the use of diurnal IOP measurement is useful in several clinical scenarios. In eyes suggestive of primary open-angle glaucoma but whose sporadic IOP measurements are always within normal range, diurnal testing may demonstrate an abnormal elevation in IOP, which help confirm the diagnosis and document peak IOP on which to base my therapy. In glaucomatous eyes with normal IOP on sporadic office measurement but whose nerves or visual fields are deteriorating, diurnal IOP measurement often demonstrate IOPs peaking above the sporadic measurements, and thus prove to both physician and patient the necessity for increasing therapy. Additionally, in eyes with very advanced glaucoma precluding monitoring by fields or disc photography, the use of diurnal IOP is an important measure to monitor for progression.

The authors have demonstrated that if the diurnal IOP measurements are normal on 1 day, it does not prove it is normal on a subsequent day. However, if the IOP does spike out of the habitual or normal range, then such a diurnal IOP measurement is valuable to more exactly evaluate that eye. Like many tests in medicine, diurnal monitoring may only be useful if an abnormality is found but that does not reduce its value, especially in a test where the cost is minor, and there are no possible major complications.

The fact that this test is not repeatable over the short term does not negate its value. Many tests in medicine are complicated by repeatability issues, but it does not mean they are not valuable in clinical practice. A perfect example in ophthalmology is visual field testing. We know such data is plagued by both reliability and reproducibility problems, but that does not mean the data is not useful. The data obtained in both IOP monitoring and visual field examination would have greater value if they were always reliable and reproducible, but we have to do the best with what we have. Until technology provides the clinician with noninvasive, 24-hour IOP monitoring, we will have to use office IOP measurements. In my opinion, obtaining systematic IOP measurements, even if not repeatable over the short term, is still better in selected cases than sporadic measurements. My routine is to measure the IOP at 0730, 1230, and 1630 hours; this is obviously not as extensive as this study, but is acceptable to most patients in that they can leave the office and simply return for the brief IOP check.

I was glad that in their discussion the authors acknowledge the clinical value of diurnal IOP measurements. Nevertheless, I am concerned that an unintended result of this study may be to discourage the use of diurnal IOP monitoring in practice, and I wish to emphasize the value of such testing from a practicing clinician's point of view.

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Reference

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Author reply

Dear Editor:
We entirely agree and thank Dr. Feibel for his thoughtful consideration of our recent study. For all of the reasons delineated by Dr. Feibel, assessment of diurnal intraocular pressure (IOP) variation remains an important component of the evaluation of patients who have or are suspected of having glaucoma. The take-home lesson from our study is that a diurnal IOP curve on any given day may not tell the whole story. As diurnal IOP variation often is different from day to day, the absence of an IOP spike on a particular day does not preclude the possibility of a daytime spike on a different day. Unfortunately, the optimal number and timing of IOP measurements necessary to adequately characterize IOP variation has not yet been established. This in no way lessens the value of diurnal IOP curve assessment, but does introduce a caution as a single-day diurnal IOP curve may not tell us as much as we might hope about IOP variation on other days.

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CF101 for Dry Eye

Dear Editor:
We read with great interest the article by Avni et al[1] on treatment of dry eye syndrome with orally administered CF101. It is indeed a novel therapy for management of signs and symptoms of such a chronic disorder. However, there are a few areas concerning the methodology and results where we have concerns and ask for clarification.

Numerous scales, based on varied parameters, have been described in literature for grading the severity of dry eye. The assignment of a patient to a moderate-to-severe grade based on a Schirmer's value of <7 mm at 5 minutes and fluorescein-based dry eye grading by the authors, should have been referenced. Also, the utility of Schirmer's test 1 (ST1) for grading the superficial punctuate keratitis (SPKs) needs further explanation. Categorization of the Schirmer's value, instead of using it as a continuous data, would not only reduce the "within the subject variability," but also reduce the large interobserver variability of the test and in

turn improve the validity of the study.[2] Since the underlying etiology of dry eye has a large bearing on the final outcome on therapy, the authors[1] could have detailed the method of randomization used to ensure the comparability of the 2 groups at the baseline.

The improvement in the fluorescein staining (FS) score and quality of tears (increased tear meniscus [TM] and break-up time [BUT]) at the end of 12 weeks, without improvement in ST1 value without anesthesia, suggests the feedback loop between the ocular surface and lacrimal gland is still hypothetical.

The distribution of A3 receptors in human eye on the ocular surface has not been proven.[3] Hence, the attribution of improvement in fluid and mucin secretion on the ocular surface to the interaction with channels via A3A receptors, seems to be an extrapolation beyond the data. The improvement in the corneal staining and tear break-up time (TBUT) in the study group may in fact be due to reduced inflammation on the ocular surface following direct interaction between CF101 and its receptors on inflammatory cells. However, a histological proof of reduction of inflammation would be more convincing.

Subjective assessment and quality of life analysis using questionnaire in chronic disorders like dry eye is paramount to validate the advantage of such a modality of therapy. In the present study,[1] despite the documented objective improvement in the severity of disease, there was no subjective improvement in symptoms or dry eye symptom score (DESS). This defeats the main goal of dry eye therapy to provide symptomatic relief. Possible explanation for this could be that DESS questionnaire was validated against disease severity (based on both the physician's assessment of severity and the composite disease severity score) and the scales used in that study for grading of ST1 values and FS were different from what has been used by authors herein.[4]

In conclusion, CF101 can be potential candidate for treatment of signs and symptoms of the multifactorial dry eye disorder and reduce dependency of the patients of moderate-to-severe dry eye on tear supplements. We look forward to long-term studies confirming the safety and efficacy of this agent for dry eye disease.

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Author reply

Dear Editor:

We thank Dr. Ashar and colleagues for their commentary on our article, and appreciate the opportunity to address their observations.

Dry eye syndrome is notoriously difficult to quantify, classify, and monitor. In 2007, the DEWS Diagnostic Methodology Subcommittee identified over 70 tests reported to diagnose and follow dry eye patients, and presented 18 alternative dry eye diagnostic templates[1] indicating to us that there is no ideal test battery and no consensus in the field regarding optimal evaluation techniques. Given that situation, we selected a series of tests that were practical, efficient, clinically relevant, and sufficiently sensitive to indicate the presence of clinical effect.

Dry eye syndrome is considered an inflammatory clinical situation,[2] and there are many anti-inflammatory therapies in clinical use that target inflammatory mechanistic pathways, such as corticosteroids, cyclosporine, tetracyclines, and essential fatty acids.[3] Furthermore, there are extensive nonclinical and clinical data showing that CF101 exerts anti-inflammatory effects through A_3AR agonism.[3–5] We would further like to point out that CF101, as a systemic therapy, could exert a treatment benefit in dry eye patients by affecting other tissues, e.g., immune effectors cells.

In later-stage trials, we intend to enroll larger populations to better define efficacy; stratify patients with respect to markers of disease severity; use the most objective and standardized test methodology available; and treat patients for longer durations to maximize the opportunity to provide symptomatic benefit.

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