Clinical and Antiviral Efficacy of an Ophthalmic Formulation of Dexamethasone Povidone-Iodine in a Rabbit Model of Adenoviral Keratoconjunctivitis

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PURPOSE. To determine the efficacy of a new formulation of topical dexamethasone 0.1%/povidone-iodine 0.4% (FST-100) in reducing clinical symptoms and infectious viral titers in a rabbit model of adenoviral keratoconjunctivitis.

METHODS. Rabbit corneas were inoculated bilaterally with $2 \times 10^7$ plaque-forming-units (PFU) of adenovirus type 5 (Ad5) after corneal scarification. Animals were randomized 1:1:1:1 (five rabbits per group) to FST-100, 0.5% cidofovir, tobramycin/dexamethasone (Tobradex; Alcon Laboratories, Fort Worth, TX) ophthalmic suspension, and balanced salt solution (BSS; Alcon Laboratories). Treatment began 12 hours after viral inoculation and continued for 7 consecutive days. The eyes were clinically scored daily for scleral inflammation (injection), ocular neovascularization, eyelid inflammation (redness), friability of vasculature, inflammatory discharge (pus), and epiphora (excessive tearing). Eye swabs were collected daily before treatment for the duration of the study. Virus was eluted from the swabs and PFU determined by titration on human A549 cells, according to standard procedures.

RESULTS. The FST-100 treatment resulted in significantly lower clinical scores ($P < 0.05$) than did the other treatments. The 0.5% cidofovir exhibited the most ocular toxicity compared with FST-100, tobramycin/dexamethasone, and balanced salt solution treatments. FST-100 and 0.5% cidofovir significantly ($P < 0.05$) reduced viral titers compared with tobramycin/dexamethasone or balanced salt solution.

CONCLUSIONS. FST-100 was the most efficacious in minimizing the clinical symptoms of adenovirus infection in rabbit eyes. FST-100 and 0.5% cidofovir were both equally effective in reducing viral titers and decreasing the duration of viral shedding. By providing symptomatic relief in addition to reducing infectious virus titers, FST-100 should be a valuable addition to treatment of epidemic adenoviral keratoconjunctivitis. (Invest Ophthalmol Vis Sci. 2011; 52:339–344) doi:10.1167/iovs.10-5944

A new efficacious antiviral therapy with a favorable therapeutic index is needed for acute infections caused by human adenovirus (Ad5). Ad5 is a moderately large (~90 nm in diameter), very stable, double-stranded DNA virus. The Ad5 family comprises at least 51 serotypes, subdivided into A to F species.1 Although infections are typically self-limiting, adenoviruses are extraordinarily infectious and are associated with community and nosocomial epidemics, especially conjunctivitis, in the United States and worldwide.2–4 Ad5 infections often lead to visual damage. Such outbreaks can be costly because of lost productivity; severe epidemics have necessitated the closing of facilities such as hospitals, schools, and nurseries.5 Epidemic adenoviral keratoconjunctivitis (EKC) typically is a self-limiting disease that resolves in approximately 2 weeks. However, given the disproportionate morbidity and potential economic impact associated with an outbreak of EKC, a therapeutic agent that reduces clinical symptoms of EKC and minimizes shedding of infectious virus would be desirable. Currently, no specific antidiadenoviral drug is available for the treatment of ocular adenoviral infection. Although numerous therapeutic agents have been assessed for adenoviral keratoconjunctivitis, none of the candidate drugs has been approved for the treatment of adenoviral eye disease by the U.S. Food and Drug Administration (FDA).6–8 However, the clinical trials websites for Alcon Research9 and Foresight Biotherapeutics9 note ongoing clinical trials for ocular antidiadenoviral agents.

Various antiviral agents effective against DNA viruses have been evaluated as treatments for EKC.10,11 Many reports document the inhibition of Ad5 replication in vitro by cidofovir,12,13 and another similar drug, the anti-HIV nucleoside reverse transcriptase inhibitor (NRTI) zalcitabine, or 2’,3’dideoxyxycytidine (ddC).14,15 Cidofovir has shown some limited efficacy in clinical trials, as indicated by a lower frequency of severe corneal opacities in individuals with adenoviral keratoconjunctivitis, although dose-dependent toxicity has been observed.16 Cidofovir has also shown success in the treatment of Ad5 eye infection in the New Zealand White (NZW) rabbit ocular model.17 Two anti-HIV NRTIs, ddC and stavudine (Zerit,
or d4T; Bristol-Meyers Squibb, New York, NY), showed significant antiadenoviral activity in vitro.18 The FDA has approved ddC for the treatment of HIV (Hivid; Roche Laboratories, Indianapolis, IN), but Roche discontinued the production and distribution of ddC in December 2006. A recent study evaluated ddC+cidofovir as a standard against a panel of ocular adenovirus serotypes and in a rabbit Ad5 replication ocular model and demonstrated potent antiadenovirus activity in vitro and in vivo.19 A recent study of the adverse effects of the potential antiadenoviral agent cidofovir and the anti-HIV agents ddC and d4T in uninfected eyes and ocular adnexa of healthy female Japanese albino rabbits reported some toxicity associated mainly with cidofovir.20 In a separate study, ddC was more cytotoxic than cidofovir.19 Thus, the toxicity in these animal studies reduces the suitability of either cidofovir or ddC: for use as an ocular therapeutic agent for EKC in humans.

Case studies on the nucleoside analogue ribavirin for systemic adenoviral infection have yielded inconsistent results,21,22 because among species A to F, only C serotypes are contagious and in anesthetic is promising as a suitable therapeutic agent for the treatment of EKC. Dexamethasone is a potent, well-tolerated steroid26,27 that has been used extensively as a topical ophthalmic agent alone and in combination regimens.28–30 Povidone-iodine is an antiseptic extensively used in preoperative antisepsis. In this study, FST-100 was compared for a 0.5% or 1.0% concentrations of povidone-iodine on the rabbit cornea administration by conjunctival sac instillation for preoperative antisepsis. This proprietary mixture containing a steroid and an antiseptic is promising as a suitable therapeutic agent for the treatment of EKC. Dexamethasone is a potent, well-tolerated steroid26,27 that has been used extensively as a topical ophthalmic agent alone and in combination regimens.28–30 Povidone-iodine is an antiseptic extensively used in preparation for general surgery, ophthalmic purposes, and laboratory disinfection.31–37 Dilute povidone-iodine solutions inhibit numerous viruses, bacteria, fungi, and some other parasites.38,39 Jang et al.40 have reported the safety and feasibility of the use of 0.5% or 1.0% concentrations of povidone-iodine on the rabbit cornea administration through conjunctival sac instillation for preoperative antisepsis. In this study, FST-100 was compared for its therapeutic efficacy against 0.5% cidofovir with two controls, tobramycin/dexamethasone (Tobradex; Alcon Laboratories, Fort Worth, TX) and balanced salt solution (BSS; Alcon Laboratories), in a rabbit model of adenoviral keratoconjunctivitis.

### MATERIALS AND METHODS

#### Rabbits, Virus, and Infection

All animal procedures adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and the NIH Principles of Laboratory Animal Care, using a protocol approved by the LSU Health Sciences Center Institutional Animal Care and Use Committee. Corneas of 20 NZW rabbits (6–8 lb) were scarified with a 3 × 3 cross-hatch pattern scratch (topical anesthesia of proparacaine hydrochloride ophthalmic solution USP 0.5% was administered; Bausch & Lomb Inc., Tampa, FL), and then the corneas were inoculated with the Ad5 strain (kindly donated by Eric Romanowski [Charles T. Campbell Ophthalmic Microbiology Laboratory, University of Pittsburgh School of Medicine, Pittsburgh, PA]) at 2 × 10⁶ PFU/eye. The animals were then randomly assigned to one of four treatment groups (five rabbits/group): FST-100; 0.5% cidofovir; 0.3% tobramycin/0.1% dexamethasone (Tobradex; Alcon Laboratories); or balanced salt solution (BSS; Alcon Laboratories).

A slit lamp examination was performed daily before drug treatment. Treatments consisted of 50-μL drops/eye applied according to the following schedules: FST-100 (four times a day, every 3 hours), 0.5% cidofovir (two times a day, every 8 hours), 0.3% tobramycin/0.1% dexamethasone (four times a day, every 3 hours), or balanced salt solution (four times a day, every 3 hours). The drug solutions for the topical applications were stored in brown sterile glass bottles and separately dispensed with disposable pipettes.

#### Infectious Virus Titer

Tears were collected daily from the eyes under the eyelids and nictitating membranes of each rabbit with a cotton swab, starting 3 hours after infection; subsequently, the swabs were taken daily in the early morning before administration of drugs over a 10-day period. Drug treatment began 12 hours after viral inoculation and continued for 24, 48, 72, 96, 120, 144, and 168 hours. Virus was eluted from the swabs with RPMI 1640 medium (1 mL; 1×, without I-glutamine; Cellgro, Mediatech Inc., Manassas, VA) and kept at −80°C overnight or until ready for use. Volumes of 200 μL of 10-fold serial dilutions of original eluate/swab were plated in triplicate to individual wells of a 24-well plate containing subconfluent A549 cells and allowed to incubate for 1 hour. Subsequently, excess media were decanted and an overlay of RPMI 1640 containing 0.5% methylcellulose was added to each well. Plates were incubated at 37°C and 5% CO₂ for 3 days, after which monolayers were fixed with 10% formaldehyde, washed, and stained with crystal violet (Hucker’s modified solution diluted 1:10 with 20% ethanol and 80% H₂O), and the plaques were counted.

### Table 1. Criteria for Scoring Ocular Disease

<table>
<thead>
<tr>
<th>Ocular Parameters (Measure)</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
<th>+3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyelid inflammation</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Scleral erosion</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td>Ocular neovascularization (%)</td>
<td>0 ≤25%</td>
<td>26%–74%</td>
<td>≥75%</td>
<td></td>
</tr>
<tr>
<td>Friability of vasculature</td>
<td>Absent</td>
<td>Reddish tinge on swab</td>
<td>~50% of swab red</td>
<td>&gt;50% of swab red</td>
</tr>
<tr>
<td>Inflammatory discharge</td>
<td>Absent</td>
<td>Slight</td>
<td>Moderate</td>
<td>Profuse</td>
</tr>
<tr>
<td>Epiphora</td>
<td>Absent</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
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Clinical symptoms were scored by two independent observers using the scoring system described in Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5944/-DCSupplemental. The six parameters listed were assessed. Each parameter was scored 0 (no disease) to +3 (maximum disease), and the sum of all six parameters represented the degree of clinical symptoms after infection and treatment. Thus, a normal, uninfected eye would have a score of 0 and an eye with the most severe disease would have a score of 18. Inflammation of the eyelids and sclera was assessed by jointly grading injection (mild [+] +1, reddish tinge, to severe [++] +3, bright red) and chemosis (mild [+] +1, localized swelling, to severe [++] +3, grossly edematous). Corneal neovascularization was determined by the percentage of corneal surface area affected by in growth of blood vessels. The friability of ocular vasculature was determined by physical examination under and around the inside of the nictitating membrane and lower eyelid for bleeding and dabbing the ocular surface with a cotton swab. A reddish tinge on the swab was assigned a +1 whereas a +3 was represented by blood staining greater than 50% of the swab’s surface. Inflammatory discharge (i.e., pus) was graded as follows: +1, discharge localized to medial canthus; +2, discharge collecting along the lid margin; and +3, profuse discharge matting fur around the eyes (and pseudomembranes). Epiphora (i.e., tearing) was graded as follows: +1, tears pooling at lower lid margin; +2, tears flowing over lower lid and staining eyelid; +3, tears staining upper and lower lids with extension below the eye socket (pseudomembranes).
Slit Lamp Examination and Scoring of Six Clinical Parameters

After corneal Ad5 infection, the eyes were monitored daily in the early morning by two independent observers with a slit lamp microscope (Eye Cap; Haag-Streit International, Mason, OH) before administration of the drugs in a masked fashion. The severity of adenoviral keratoconjunctivitis was assessed by scoring six clinical parameters: scleral inflammation (injection), ocular neovascularization, eyelid inflammation (redness), friability of vasculature, inflammatory discharge (pus), and epiphora (excessive tearing). The clinical scoring was based on a weighted scale (Table 1), using the scoring system described in detail in Supplementary Table S1, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5944/#/DCSupplemental. Clinical scores were recorded at 3, 24, 48, 72, 96, 120, 144, 168, 192, and 240 hours after infection. The mean ± SEM clinical score was calculated from the daily cumulative of the six clinical parameters as independent events, to evaluate improvement of the rabbit eyes (Fig. 1). In addition, the cumulative score values of the six clinical parameters in each drug treatment group were weighted vertically to provide a method of comparison (Supplementary Table S2, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5944/#/DCSupplemental).

Statistical Analysis

The analysis of the various clinical scores was undertaken by use of the generalized estimating equation (GEE) approach. The experimental design provided repeated observations over time from each rabbit assigned to each treatment. This design is expected to provide data correlated within subjects. In addition, the nature of the ordinal scores used as variables is not expected to be normally distributed, because of the truncated range of values observed.

In such cases in which the normality assumption likely does not hold, different methodology must be used in the data analysis when the responses are discrete and correlated. GEEs provide a practical method with reasonable statistical efficiency to analyze such data. With the GEE, each score was analyzed separately, a multinomial distribution of the scores was assumed, and a cumulative logit link function was applied. Pair-wise comparisons of mean treatment scores were conducted by using a set of contrasts with vectors constructed to test hypotheses on the comparisons of the control score values with the other treatments (three comparisons in the case of each score).

![FIGURE 1. Line graph showing mean ± SEM ocular clinical scores of Ad5-infected rabbit eyes treated with FST-100, cidofovir, balanced salt solution (BSS; Alcon Laboratories), or 0.3% tobramycin/0.1% dexamethasone (Tobradex; Alcon Laboratories) over time. The mean ± SEM ocular clinical score is calculated from the daily cumulative of the six clinical parameters (scleral inflammation [injection], ocular neovascularization, eyelid inflammation [redness], friability of vasculature, inflammatory discharge [pus], and epiphora [excessive tearing]) per rabbit eye, indicating that a normal, uninfected eye would have a score of 0 and an eye with the most severe disease would have a score of 18.](image1)

![FIGURE 2. Line graph showing mean ± SEM PFU reduction by FST-100, cidofovir, balanced salt solution (BSS; Alcon Laboratories), or 0.3% tobramycin/0.1% dexamethasone (Tobradex; Alcon Laboratories). When the SEM error bars are not visible, they are too small to be seen. Swabs from infected eyes were eluted and 200 μL of 10-fold serial dilutions of the original eluate/swab plated on near-confluent A549 cells with methylcellulose overlay. Fixed cells were stained with Hucker’s modified crystal violet solution after 3 days and the plaques counted.](image2)
RESULTS

Clinical Improvement in FST-100–Treated Ad5-Infected Eyes

The FST-100 treatment group had the lowest scores from the daily cumulative of the six clinical parameters calculated as independent events to evaluate improvement to the rabbit eyes (Fig. 1). Moreover, FST-100 was the most efficacious therapeutic agent in the treatment of the Ad5 ocular infection. FST-100 significantly reduced the debilitating effects of the adenoviral symptomatic clinical parameters: scleral inflammation (injection), ocular neovascularization, eyelid inflammation (redness), friability of vascularule, inflammatory discharge, and epiphora (Fig. 1). Evaluation of cumulative clinical parameters indicated that FST-100 had the lowest clinical indices with a relative difference index set at 100% (Supplementary Table S2, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5944/-/DCSupplemental). By comparison, balanced salt solution (BSS) at +490%, 0.3% tobramycin/0.1% dexamethasone (Tobradex) at +320%, and 0.5% cidofovir at +920% showed only incremental effects of treatment (Supplementary Table S2, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5944/-/DCSupplemental). 0.3% tobramycin/0.1% dexamethasone also demonstrated some superior to 0.5% cidofovir by moderately reducing clinical symptoms (Fig. 1; Supplementary Table S2, http://www.iovs.org/lookup/suppl/doi:10.1167/iovs.10-5944/-/DCSupplemental).

Reduction of Viral Titers in FST-100– and 0.5% Cidofovir–Treated Ad5-Infected Eyes

The 0.5% cidofovir caused the most rapid decrease in viral titers (Fig. 2); however, there was no significant difference compared with FST-100, indicating that both drugs were equally effective in reducing adenoviral titers (Fig. 2). The error bars indicate that there was no statistical significance between the viral titers with 0.5% cidofovir and FST-100 treatments; however, these were significantly distinct from the titers with 0.3% tobramycin/0.1% dexamethasone and balanced salt solution. 0.3% tobramycin/0.1% dexamethasone in particular showed an initial decrease of around 10⁶ PFU then the viral titers went back up and remained constant through the remainder of the scoring period, indicating maintenance of fairly constant amounts of PFU over the treatment period and generally no suppression in Ad5 replication (Fig. 2).53 Balanced salt solution initially had high adenoviral titers but was self-limiting as indicated by the eyes that were cleared of Ad5 with time (Fig. 2).

Clinical Resolution in FST-100–Treated Ad5-Infected Eyes

FST-100 was the most efficacious therapeutic agent in the treatment of ocular inflammation, as it alone significantly reduced all six clinical parameters (Tables 2A, 2B; Fig. 1) and also controlled adenoviral titers equivalent to those of 0.5% cidofovir and greater than those of the 0.3% tobramycin/0.1% dexamethasone or balanced salt solution treatment groups (Fig. 2). Physical examination of FST-100–treated rabbit eyes at 168 hours showed no visible disease (Figs. 3IA–3IF) compared with

![Image](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932967/ on 07/15/2018)
severe clinical symptoms shown by eyes treated with cidofovir (Figs. 3IIA–3IIIF, balanced salt solution (Fig. 3IIIA–3IIIF), and 0.5% tobramycin/0.1% dexamethasone (Fig. 3IVA–3IVF).

**DISCUSSION**

The pilot open-label human study by Pelletier et al. documented the efficacy of this new formulation of ophthalmic suspension containing podivone-iodine 0.4%+ dexamethasone 1% in the treatment of adenoviral keratoconjunctivitis. This small, open-label human clinical trial was conducted in light of the extensive ophthalmic use of these two drugs: podivone-iodine34–37 and dexamethasone.25,28–30 In our controlled in vivo study of a NZW rabbit model of adenoviral keratoconjunctivitis, we demonstrated the clinical and antiviral benefits of FST-100. Two experimental animal models of infected adenoviral keratoconjunctivitis are currently available.44,45 The NZW rabbit model was used to demonstrate that the Ad5 species C serotypes 1, 2, 5, 6, and 14 could replicate and cause productive infections in the eyes, but types 8 and 19 could not.44,46 Epidemic keratoconjunctivitis in the rabbit eyes is mainly produced by Ad5 species D serotypes 8, 19, and 37.44 Further, pharyngoconjunctival fever is caused by Ad5 serotypes 3 and 7, which belong to species B.44 The second model is a cotton rat model that can be infected with 5, 8, and 37 among the many serotypes of Ad5.45,47,48

In our study of Ad5-infected rabbits, FST-100 was given topically four times daily in the treatment group for 7 days parallel to an equally weighted group for 0.5% cidofovir treatment that was administered twice daily for the same duration. 0.5% tobramycin/0.1% dexamethasone and balanced salt solution were given four times daily for 7 days. The 0.5% cidofovir treatment regimen of 14 doses totaling 3.5 mg theoretically is a low concentration tested in vivo and should have the least adverse effects compared; Gordon et al. reported the direct toxicity of cidofovir in uninfected animals and found that clinically significant local ocular toxicity occurred almost always at a total dose exceeding 15 mg administered for a period of 10 days. Inoue et al. recently evaluated the adverse effect of 1% cidofovir administered 4× daily for 14 days (56 doses) totaling 28 mg. There was significant eyelid redness in most of the animals in the 1% cidofovir group, as well as in the dDC- and d4T-treated groups on day 14.20 There was significant hyperemia in all conjunctivae of the cidofovir-treated group on days 7 and 14, in the d4T-treated group after day 7, and in the dDC-treated group only on day 10 in comparison with the control group.20 In the present study, we used 0.5% cidofovir totaling 3.5 mg that was eightfold less than the total 28 mg used by Inoue et al., however, this low dosage showed severe local ocular toxicity in vivo (Figs. 1, 3II). The drug total of 3.5 mg of cidofovir was also substantially below the acceptable limit proposed by Gordon et al.20 The Ad5 infection was one of the primary factors for the observed eyelid redness and hyperemia. The balanced salt solution (Fig. 3III) and 0.3% tobramycin/0.1% dexamethasone (Fig. 3IV) treatment groups were similarly symptomatic; however, the symptoms were milder than the severity observed in the 0.5% cidofovir-treated group (Fig. 3II). Cidofovir given as a topical drug in uninfected animals induced blockage of the nasolacrimal drainage system and lacrimation.49 Further, Inoue et al.20 reported a significant narrowing of the lacrimal canaliculus without complete obstruction of the nasolacrimal duct in the 1% cidofovir-treated group. Second, results of a histopathologic study suggested that the local side effects could have been induced by allergic inflammation rather than by cytotoxic necrotic reaction.20

Our study evaluated FST-100 using infected rabbits in an approach that weighted 0.5% cidofovir according to the latter’s known favorable and toxic adverse effects, together with the balanced salt solution and 0.3% tobramycin/0.1% dexamethasone controls. The results of this weighted approach allowed evaluation of FST-100 for its therapeutic effect in a straightforward manner. Our collective results indicate that FST-100 is the safest drug of choice to yield excellent clinical resolution (Figs. 1, 2, 3), safer than cidofovir (0.5% or 1%), if used for a shorter period or the same length of time, indicating its potential as topical therapy for patients with adenoviral keratoconjunctivitis alone or with secondary bacterial infections. Of interest, 0.3% tobramycin/0.1% dexamethasone treatment, although moderately effective in reducing clinical symptoms, had an opposite effect on viral titers, as there was no suppression of Ad5 replication. Our data show that treatment with 0.3% tobramycin/0.1% dexamethasone prolonged the time until clearance and prevented Ad5 replication from being self-limiting. Often the use of steroids in the eye is contraindicated for viral infections because they exacerbate the replication of virus and the inhibition of immune clearance, as shown by the 0.3% tobramycin/0.1% dexamethasone data. Although FST-100 contains dexamethasone, much like 0.3% tobramycin/0.1% dexamethasone, the two data sets are polar opposites, indicating that the antiviral activities of FST-100 counteract the effects of the dexamethasone alone. Thus, the antiseptic effect of FST-100 is capable of inhibiting replication of virus yet mitigating the potential for toxicity in contrast to results of a study by Romanowski et al., who evaluated topical combinations of corticosteroids and cidofovir in the Ad5 ocular NZW model and reported the reversal of the antiviral effect of cidofovir.

Currently, the favorable human data in combination with our in vivo results provide a strong impetus for a human phase III clinical trial to test the efficacy of this drug in a larger group and also to evaluate complete safety to properly establish the therapeutic benefit versus adverse effect.25 In conclusion, our results indicate that FST-100 showed no toxicity or irritation to the ocular surface compared with cidofovir. Thus, FST-100 has the potential to become the drug of choice for adenoviral keratoconjunctivitis in humans. The additional benefits of the antimicrobial activity of podivone-iodine make FST-100 useful as well in an acute adenoviral ocular infection in which there is a secondary bacterial infection. The FST-100 formulation containing dexamethasone and a powerful antiseptic (podivone-iodine) could be most effective in the treatment of the more serious form of infection, EKC, because dilute podivone-iodine solutions kill numerous viruses, including all animal viruses, bacteria, fungi, and some other parasites and is safe and tolerable.

**Acknowledgments**

The authors thank Michael Weiser (Actin Biomed and Foresight Biotherapeutics Inc., New York, NY) for his important contribution in evaluating viral and clinical assay data.

**References**


