

# The ocular distribution of $^{14}\text{C}$ -labeled bromfenac ophthalmic solution 0.07% in a rabbit model

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**Purpose:** To evaluate the ocular distribution of an advanced formulation of bromfenac ophthalmic solution. Two studies were conducted in rabbits: 1) a 12-hour parallel-group study comparing the ocular distribution of  $^{14}\text{C}$ -bromfenac ophthalmic solution 0.07%, pH 7.8 with that of  $^{14}\text{C}$ -bromfenac ophthalmic solution 0.09%, pH 8.3, and 2) a 24-hour study evaluating the ocular distribution of  $^{14}\text{C}$ -bromfenac ophthalmic solution 0.07%, pH 7.8.

**Methods:** In the 12-hour study, rabbits were randomized to receive 50  $\mu\text{L}$  of  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 or 50  $\mu\text{L}$   $^{14}\text{C}$ -bromfenac 0.09%, pH 8.3 in one eye, whereas, in the 24-hour, study both eyes received 50  $\mu\text{L}$  of  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8. Ocular tissues were collected at 1, 2, 4, 8, 12 (both studies) and 24 hours (second study only) following drug instillation, and tissue radioactivity was determined using liquid scintillation chromatography.

**Results:** Measureable levels of bromfenac were observed in all ocular tissues, with the exception of vitreous humor, regardless of formulation. In the 12-hour study, high concentrations of  $^{14}\text{C}$ -bromfenac were found in the sclera, followed by the iris/ciliary body, aqueous humor, choroid, retina, and lens. There was no significant difference between the bromfenac 0.07%, pH 7.8 and bromfenac 0.09%, pH 8.3 formulations in any  $^{14}\text{C}$ -bromfenac tissue levels at any time point, with the exception of in sclera at 2 hours post-instillation (0.451  $\mu\text{g}$  eq/g versus 0.302  $\mu\text{g}$  eq/g, respectively,  $P < 0.001$ ). There was also no significant difference in the total amount of  $^{14}\text{C}$ -bromfenac in the tissues evaluated following instillation of the two formulations. In the 24-hour study evaluating bromfenac 0.07%, pH 7.8 only, high concentrations of  $^{14}\text{C}$ -bromfenac were found 1 hour post-instillation in the cornea (2.402  $\mu\text{g}$  eq/g) and conjunctiva (1.049  $\mu\text{g}$  eq/g), two tissues not evaluated in the 12-hour study. The rank order of  $^{14}\text{C}$ -bromfenac levels in the other ocular tissues was the same as that observed in the 12-hour study, with measureable amounts of  $^{14}\text{C}$ -bromfenac detected through 24 hours in all tissues with the exception of vitreous humor.

**Conclusion:** Bromfenac ophthalmic solution 0.07%, pH 7.8 readily penetrated ocular tissues with levels similar to those of bromfenac ophthalmic solution 0.09%, pH 8.3.

**Keywords:** penetration, topical NSAIDs, pharmacokinetics, eye, pH

## Introduction

Topical ophthalmic drugs are often reformulated for improved bioavailability and/or reduced dosing frequency. Most often this is accomplished by increasing the concentration of the active ingredient in the formulation. Another approach is to modify the vehicle without increasing the concentration.<sup>1</sup> Recently, bromfenac ophthalmic solution was reformulated with a lower pH to allow for a decreased concentration of the active ingredient while maintaining high intraocular tissue exposure. In order to provide clinicians insight into the applicability of the modified bromfenac formulation in the management of various ocular disorders, studies were conducted to evaluate the ocular penetration of bromfenac in the modified formulation and compare it to a previously marketed reference formulation.

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Topical nonsteroidal anti-inflammatory drugs (NSAIDs) are routinely used for treatment of inflammation and pain secondary to cataract surgery, and are sometimes preferred over topical corticosteroids to avoid steroid-associated adverse events such as elevated intraocular pressure and cataract formation.<sup>2-4</sup> In the United States, bromfenac ophthalmic 0.09% solution is a topical NSAID indicated for the treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract extraction. The 0.09% formulation (or 0.1% when labeled as the salt form) has been shown to be as effective as betamethasone in minimizing inflammation following cataract surgery.<sup>5</sup> In April 2013, Bausch + Lomb gained US Food and Drug Administration (FDA) approval for bromfenac 0.07% (Prolensa<sup>®</sup>; Bausch + Lomb, Irvine, CA, USA), a once-daily, advanced formulation of bromfenac ophthalmic solution.<sup>6</sup> Prolensa<sup>®</sup> was reformulated from bromfenac 0.09% (Bromday<sup>®</sup>; Bausch + Lomb) to achieve similar ocular bioavailability with a lower concentration of active drug, thereby ensuring similar clinical efficacy to Bromday<sup>®</sup> but with reduced exposure of the surgically compromised ocular surface to the drug. In order to lower the concentration yet maintain the same degree of ocular penetration, the pH of the formulation was reduced from 8.3 (Bromday<sup>®</sup>) to 7.8 (Prolensa<sup>®</sup>). Bromfenac, like most NSAIDs, is a weakly acidic drug.<sup>7</sup> Decreasing the pH of the formulation increases the unionized fraction of the drug, which, in turn, enhances ocular penetration.<sup>7</sup>

NSAIDs have anti-inflammatory properties mediated by the inhibition of the cyclooxygenase (COX) pathway and prostaglandin (PG) synthesis. PGs, which increase after cataract surgery, disrupt the blood–aqueous humor barrier and increase vascular permeability, vasodilation, and intraocular pressure, leading to ocular inflammation.<sup>8,9</sup> Studies have shown that the COX-2 enzyme, considered the primary mediator of ocular inflammation,<sup>10</sup> is upregulated in animal models of ocular inflammation and ocular injury.<sup>11,12</sup>

In order to reduce inflammation effectively, ophthalmic NSAIDs need to both penetrate the affected tissues and bind to the COX-2 enzyme. A study of the physicochemical properties of amfenac and its derivatives found that the addition of a substituent group to the aromatic ring of the molecule decreased, while the addition of a halogen group (Br>I>Cl>F) to the 4'-position of the aromatic ring increased anti-inflammatory potency.<sup>13</sup> The presence of a bromine in the 4'-position, as in bromfenac, was found to improve in vitro and in vivo potency, absorption across the cornea, and penetration into ocular tissues.<sup>13-15</sup> Bromfenac is a selective COX-2 inhibitor with an IC<sub>50</sub> approximately

32 times more active against COX-2 than COX-1 (IC<sub>50</sub> of 0.0066 μM and 0.210 μM, respectively),<sup>16</sup> and it has been shown in an animal model to significantly prevent PGE<sub>2</sub> production compared with nepafenac (*P*<0.05).<sup>17</sup> Bromfenac is also highly lipophilic, with a C<sub>logP</sub> (octanol/water partition coefficient) of 2.23, which is higher than that of amfenac (1.23), suggesting that bromfenac may have increased penetration into ocular tissues and potentially a more rapid onset of action.<sup>15</sup> A pharmacokinetic study in patients undergoing cataract surgery showed that bromfenac was absorbed within 30 minutes following instillation of bromfenac ophthalmic solution 0.1%, with a peak aqueous humor concentration at 2.5 to 3 hours after instillation.<sup>18</sup> In addition, a previous animal study demonstrated that bromfenac 0.09%, pH 8.3 readily penetrates ocular tissues.<sup>19</sup>

The objective of the current two studies was to evaluate the ocular distribution of the new modified formulation of bromfenac ophthalmic solution. The first study evaluated the 12-hour ocular distribution profile of <sup>14</sup>C-bromfenac ophthalmic solution 0.07%, pH 7.8 compared with <sup>14</sup>C-bromfenac ophthalmic solution 0.09%, pH 8.3, while the second study evaluated the 24-hour ocular distribution of <sup>14</sup>C-bromfenac ophthalmic solution 0.07%, pH 7.8 to confirm sustained ocular penetration with once-daily dosing.

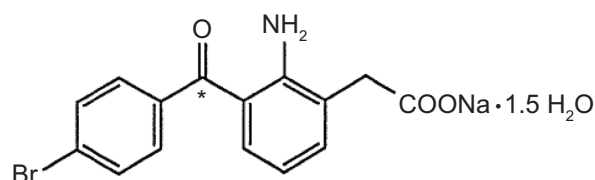
## Methods

Two separate preclinical studies were performed at the Biological Test Center ([BTC] Irvine, CA, USA) using similar protocols. Each study complied with the animal welfare policies of the BTC, was approved by the Institutional Animal Care and Use Committee (IACUC), and conformed to the ARVO (Association for Research in Vision and Ophthalmology) “Statement on the Use of Animals in Ophthalmic and Visual Research.”

## Test article

The <sup>14</sup>C-bromfenac was manufactured by Daiichi Pure Chemicals Co., Ltd., and provided by Senju Pharmaceuticals Co., Ltd., (Osaka, Japan). It was determined to be 98.3% pure by high-performance liquid chromatography (HPLC). The radiolabeled carbon atom was that of the carbonyl within the bromobenzoyl group of bromfenac (Figure 1), a stable position within the molecule.

Dosing solutions were prepared by adding <sup>14</sup>C-bromfenac to diluent to reach a concentration of 0.07%, pH 7.8 or 0.09%, pH 8.3. The resulting <sup>14</sup>C-bromfenac 0.07%, pH 7.8 and the 0.09%, pH 8.3 formulations used in the studies



**Figure 1** Molecular structure of bromfenac showing the position of the  $^{14}\text{C}$  label.  
**Note:**  $^{14}\text{C}$ .

were identical to the marketed Prolensa<sup>®</sup> and Bromday<sup>®</sup> formulations, respectively, with the exception of the inclusion of  $^{14}\text{C}$ -bromfenac. Following dosing, dosing solutions were reanalyzed by HPLC to confirm radioactive purity; all samples were determined to be 95% to 99% pure.

## Animals

In both studies, female New Zealand White rabbits were obtained from The Rabbit Source (Ramona, CA, USA). Animals were at least 12 weeks of age and weighed 1.9 to 3.6 kg at the time of dosing. Animals were housed in individual cages and identified with ear tags and cage cards.

## Pretreatment examination and dosing procedures

Prior to placement in the study, each animal underwent a pretreatment ophthalmic examination as well as a slit-lamp examination. Criteria for acceptance into the study were severity scores of  $\leq 1$  (on 0–3 or 0–4 scales) for conjunctival congestion and swelling, and the absence of any other slit-lamp signs. Prior to dosing, animals were weighed and randomly assigned to a study group. For the 12-hour study, animals were divided into groups receiving either  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 or  $^{14}\text{C}$ -bromfenac 0.09%, pH 8.3 for collection of ocular tissues at one of five different time points (1, 2, 4, 8, and 12 hours). For the 24-hour study, animals were divided into groups receiving  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 for collection of ocular tissue at one of six different time points (1, 2, 4, 8, 12, and 24 hours). There was no comparator arm in the 24-hour study.

On day 1 of each study, 50  $\mu\text{L}$  of  $^{14}\text{C}$ -bromfenac dosing solution was administered into the conjunctival sac of each animal using a calibrated digital pipette, and the time of dose administration was noted. The eyelids were held closed post-dose for 5–10 seconds. Actual dose in mg and  $\mu\text{Ci}$  were used in all subsequent calculations.

In the 12-hour parallel-group study, animals received either  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 or  $^{14}\text{C}$ -bromfenac 0.09%, pH 8.3 in one eye. The specific activity of bromfenac in these

formulations was 528,494 dpm/ $\mu\text{g}$  (or 0.23  $\mu\text{Ci}/\mu\text{g}$ ) and 359,952 dpm/ $\mu\text{g}$  (or 0.16  $\mu\text{Ci}/\mu\text{g}$ ), respectively. Three rabbit eyes were dosed per treatment per time point for a total of 15 eyes dosed for each test agent. Animals were euthanized by intravenous injection of a commercial euthanasia solution per the standard operating procedure of the animal facility (BTC) at predetermined time points (1 hour [ $\pm 5$  minutes], 2 hours [ $\pm 15$  minutes], 4 hours [ $\pm 15$  minutes], 8 hours [ $\pm 15$  minutes], or 12 hours [ $\pm 15$  minutes]) after instillation of test agent, and ocular tissues were immediately harvested. In the 24-hour study, animals were administered  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 only (specific activity of 411,032 dpm/ $\mu\text{g}$  or 0.18  $\mu\text{Ci}/\mu\text{g}$ ). Both eyes from three rabbits were dosed per time point over a 24-hour period for a total of six eyes dosed per time point. Animals were euthanized as described above at 1 hour ( $\pm 5$  minutes), 2 hours ( $\pm 15$  minutes), 4 hours ( $\pm 15$  minutes), 8 hours ( $\pm 15$  minutes), 12 hours ( $\pm 15$  minutes), or 24 hours ( $\pm 15$  minutes) after administration of test agent, and ocular tissues harvested.

In both studies, animals were observed for morbidity and mortality throughout the study.

## Sample processing and radioactivity measurements

Tissues harvested included the aqueous humor, vitreous humor, iris/ciliary body, lens, retina, choroid, sclera (both studies), and cornea and conjunctiva (24-hour study only). While the 12-hour study focused on the tissues most relevant to treating postoperative inflammation, the 24-hour study, conducted later, was patterned from a previously developed 24-hour drug exposure protocol<sup>19</sup> and focused on all ocular tissues and therefore also included the cornea and conjunctiva. Immediately following euthanasia, the aqueous humor was collected from the eye and frozen at  $-20^\circ\text{C}$  if not immediately analyzed. The globe was then enucleated, snap-frozen in liquid nitrogen, and stored at  $\leq -70^\circ\text{C}$  until dissection.

Iris/ciliary body, lens, retina, choroid, sclera (both studies), and cornea and conjunctiva (24-hour study only) were dissected from each eye, weighed into combustion cones, and combusted. Combusted samples were trapped in  $^{14}\text{C}$ -Cocktail (RJ Harvey, Hillsdale, NJ, USA) in liquid scintillation chromatography (LSC) vials and the amount of radioactivity was determined by LSC. To determine the amount of radioactivity in aqueous humor and vitreous humor, duplicate aliquots of each aqueous humor sample (25  $\mu\text{L}$ ) and homogenized vitreous humor sample (100  $\mu\text{L}$ ) were transferred to LSC vials and the amount of radioactivity determined following the addition of 10 mL of Insta-Gel

(Perkin-Elmer Life and Analytical Sciences, Inc., Waltham, MA, USA).

Radioactivity measurements were made using a Beckman Liquid Scintillation Spectrometer (Beckman Coulter Inc., Fullerton, CA, USA). Counting time was to a statistical accuracy of  $\pm 2\%$  or a maximum of 10 minutes, whichever came first. Background noise was automatically subtracted from each measurement and counts per minute were automatically converted to disintegrations per minute.

## Statistical analysis

To determine the specific activity (dpm/ $\mu\text{g}$ ) of  $^{14}\text{C}$ -bromfenac, the following formula was used:

$$\text{Specific activity (dpm}/\mu\text{g)} = \frac{\text{Dosing solution radioactivity (dpm/g)}}{\text{Bromfenac concentration of dosing solution } (\mu\text{g/mL})} \times \text{Dosing solution density (g/mL)} \quad (1)$$

To determine bromfenac-equivalent concentration of dosed  $^{14}\text{C}$ -bromfenac, the following formula was used:

$$\text{Bromfenac equivalent concentration } (\mu\text{g eq/g}) = \frac{\text{Sample radioactivity (dpm/g)}}{\text{Specific activity of bromfenac (dpm}/\mu\text{g)}} \quad (2)$$

Mean and standard deviation of each set of samples were used to characterize the data. Although the sample size ( $N=3$  eyes per treatment per time period) in the 12-hour study was not powered to find a specific difference, Student's *t*-tests were used to compare the groups.

## Results

### 12-hour pharmacokinetic study

Following the administration of either  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 or  $^{14}\text{C}$ -bromfenac 0.09%, pH 8.3, concentrations of bromfenac ranged from 0.000 to 0.595  $\mu\text{g eq/g}$  depending on the tissue. The highest  $^{14}\text{C}$ -bromfenac levels were found in the sclera, followed by the iris/ciliary body, aqueous humor, choroid, retina, and lens (Table 1, Figures 1 and 2). The timing of peak concentrations of radiolabeled bromfenac varied among the tissues, with peak levels being reached at 1 hour in the sclera and retina and at 2 hours in the aqueous humor, iris/ciliary body, lens, and choroid. There was a significant difference between the formulations at the 2-hour time point for scleral  $^{14}\text{C}$ -bromfenac levels, with higher levels in the animals randomized to the bromfenac 0.07%, pH 7.8 treatment group ( $P<0.001$ ). However, there were no other

between-treatment differences at any other time points in any tissue. The total amount (ie, sum) of  $^{14}\text{C}$ -bromfenac in all ocular tissues evaluated was directionally higher in the  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8 group compared with the  $^{14}\text{C}$ -bromfenac 0.09%, pH 8.3 group in four out of five time points, but the differences were not statistically significant.

### 24-hour pharmacokinetic study

After administration of  $^{14}\text{C}$ -bromfenac 0.07%, pH 7.8,  $^{14}\text{C}$ -bromfenac was detected in all tissues of the eye over a 24-hour period, with the exception of vitreous humor. As expected, the highest concentrations were seen in the cornea, followed by conjunctiva and sclera (Table 2 and Figure 3). The concentrations in all ocular tissues decreased to varying degrees over the 24-hour study period, with the exception of the lens, which exhibited little change from the 1-hour time point.

No adverse events were observed in either study.

## Discussion

Ocular inflammation following surgery arises from a complex series of intracellular signaling events involving COX-1 and COX-2 enzymes. In particular, activation of the COX-2 signaling pathway leads to the production of PGs and thromboxane A<sub>2</sub>, which ultimately alters vascular permeability by changing the function of vascular endothelial cells.<sup>8</sup> Topical NSAIDs are a class of anti-inflammatory drugs that have been used following cataract and other ocular surgeries, as well as in ocular disorders affecting the posterior chamber of the eye, due to their ability to inhibit the COX signaling pathways, thereby decreasing inflammation. In order for any topical NSAID to achieve its desired effects, the drug must penetrate the tissues of the eye, target the induced COX enzymes, and remain sustained within the tissue long enough to prevent or reduce PG effects. Once-daily dosing reduces the need for repeated applications and potentially improves patient adherence.

Bromfenac topical ophthalmic solution has been shown to quickly permeate the tissues of the eye, maintain measurable concentrations for up to 24 hours, and effectively inhibit the COX-2 signaling pathway, making it an effective NSAID in the treatment of ocular inflammation.<sup>9</sup> Several studies have compared bromfenac with other topical NSAIDs for the ability to inhibit COX-2 activity and hence inhibit inflammation. Gianni et al compared the  $\text{IC}_{50}$  values of bromfenac, diclofenac, and amfenac for purified rabbit COX-2 and found that the inhibitory effect of bromfenac on COX-2 was 3.7 times greater than that of diclofenac and 6.5 times greater

**Table 1** Concentration of <sup>14</sup>C-bromfenac in ocular tissues over 12 hours following topical administration of <sup>14</sup>C-bromfenac 0.07%, pH 7.8 or <sup>14</sup>C-bromfenac 0.09%, pH 8.3

Sample, mean (SD)	Mean (± SD) bromfenac equivalents in µg eq/g									
	1 hour		2 hours		4 hours		8 hours		12 hours	
	0.07%, pH 7.8	0.09%, pH 8.3	0.07%, pH 7.8	0.09%, pH 8.3	0.07%, pH 7.8	0.09%, pH 8.3	0.07%, pH 7.8	0.09%, pH 8.3	0.07%, pH 7.8	0.09%, pH 8.3
Aqueous humor	0.048 (0.024)	0.051 (0.017)	0.090 (0.024)	0.137 (0.063)	0.038 (0.011)	0.052 (0.021)	0.018 (0.004)	0.018 (0.015)	0.011 (0.003)	0.010 (0.005)
Vitreous humor	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.001 (0.000)
Iris/ciliary body	0.081 (0.037)	0.078 (0.027)	0.110 (0.044)	0.083 (0.013)	0.048 (0.005)	0.061 (0.016)	0.029 (0.013)	0.034 (0.017)	0.018 (0.001)	0.022 (0.009)
Lens	0.001 (0.000)	0.002 (0.001)	0.003 (0.001)	0.002 (0.001)	0.002 (0.000)	0.002 (0.000)	0.002 (0.001)	0.002 (0.002)	0.002 (0.000)	0.003 (0.003)
Retina	0.013 (0.005)	0.018 (0.005)	0.010 (0.002)	0.015 (0.003)	0.006 (0.001)	0.010 (0.004)	0.002 (0.000)	0.002 (0.001)	0.003 (0.004)	0.002 (0.001)
Choroid	0.045 (0.012)	0.058 (0.010)	0.062 (0.011)	0.083 (0.030)	0.035 (0.007)	0.043 (0.022)	0.011 (0.004)	0.010 (0.004)	0.008 (0.002)	0.008 (0.002)
Sclera	0.595 (0.156)	0.346 (0.134)	0.451 (0.028)	0.302 (0.006)	0.170 (0.026)	0.220 (0.160)	0.058 (0.019)	0.026 (0.020)	0.067 (0.045)	0.039 (0.015)
<b>Total</b>	<b>0.783</b> (0.231)	<b>0.553</b> (0.186)	<b>0.726</b> (0.088)	<b>0.623</b> (0.080)	<b>0.300</b> (0.048)	<b>0.388</b> (0.218)	<b>0.121</b> (0.005)	<b>0.092</b> (0.058)	<b>0.109</b> (0.043)	<b>0.085</b> (0.031)

**Notes:** N=15 for each treatment, three rabbits per time point. All differences between formulations were statistically insignificant at all time points with the exception of the 2-hour scleral drug level ( $P < 0.001$ ). All differences between formulations in total drug levels were statistically insignificant ( $P > 0.20$ ) using a Student's t-test, without correction for multiple comparisons.

**Abbreviation:** SD, standard deviation.

than that of amfenac.<sup>14</sup> An additional study comparing the  $IC_{50}$  of bromfenac to amfenac, diclofenac, and ketorolac using recombinant human COX-2 demonstrated that bromfenac had the greatest activity against human COX-2, followed by amfenac, ketorolac, and diclofenac.<sup>20</sup>

An advanced formulation of bromfenac ophthalmic solution was recently developed which contains a lower concentration of bromfenac at a lower pH than previous formulations. It was hypothesized that reducing the pH from 8.3 from 7.8 would allow for a lower-concentration

**Table 2** Concentration of <sup>14</sup>C-bromfenac in ocular tissues over 24 hours following topical administration of <sup>14</sup>C-bromfenac 0.07%, pH 7.8

Sample, mean (SD)	Mean (± SD) bromfenac equivalents in µg eq/g					
	1 hour	2 hours	4 hours	8 hours	12 hours	24 hours
Aqueous humor	0.057 (0.014)	0.064 (0.008)	0.049 (0.019)	0.017 (0.006)	0.006 (0.002)	0.00 (0.001)
Vitreous humor	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
Iris/ciliary body	0.077 (0.016)	0.082 (0.015)	0.058 (0.020)	0.026 (0.007)	0.017 (0.002)	0.010 (0.005)
Lens	0.001 (0.000)	0.001 (0.000)	0.001 (0.001)	0.001 (0.000)	0.001 (0.000)	0.002 (0.001)
Retina	0.012 (0.006)	0.010 (0.004)	0.007 (0.001)	0.002 (0.001)	0.001 (0.000)	0.001 (0.000)
Choroid	0.054 (0.012)	0.036 (0.012)	0.032 (0.010)	0.010 (0.005)	0.005 (0.001)	0.002 (0.001)
Sclera	0.477 (0.085)	0.265 (0.104)	0.149 (0.062)	0.075 (0.058)	0.018 (0.005)	0.009 (0.013)
Cornea	2.402 (0.534)	1.998 (0.407)	1.219 (0.529)	0.471 (0.230)	0.228 (0.092)	0.080 (0.050)
Conjunctiva	1.049 (0.138)	0.485 (0.213)	0.355 (0.181)	0.137 (0.067)	0.079 (0.056)	0.031 (0.040)

**Note:** N=3 per time point.

**Abbreviation:** SD, standard deviation.

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