Impact of Variations in Critical Quality Attributes of Brinzolamide Ophthalmic Suspensions on Preclinical Pharmacokinetics and Pharmacodynamics Following Once-Daily Topical Instillations

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Abstract

Brinzolamide ophthalmic suspensions are indicated for treatment of elevated intraocular pressure (IOP), a major risk factor for optic nerve damage and glaucomatous visual field loss. Therefore, understanding the relationship between critical quality attributes (CQAs) of these ophthalmic suspensions and their pharmacokinetic/pharmacodynamic (PK/PD) performance is critical in furtherance of safe and effective generic products for treatment of IOP. To assess the potential impact of variations in CQAs (i.e., apparent viscosity and particle size distribution, PSD) on PK/PD of brinzolamide ophthalmic suspensions, a multi-dose, parallel study with once-daily ophthalmic instillations of brinzolamide suspensions (0.5 mg/eye) was conducted for 14 days in rabbits. Ophthalmic suspensions varying in CQAs did not lead to remarkable differences in PK/PD of brinzolamide likely due to the sparser dosing regimen assessed in this study (once daily) when compared with clinical dosing recommendations for brinzolamide ophthalmic suspensions (3x day), hindering drug concentration build-up in ocular tissues and leading to confounded.

Introduction

Brinzolamide suspensions are indicated for the treatment of elevated IOP. Disturbances or obstructions of aqueous outflow are the underlying cause of IOP elevation. Brinzolamide acts at the iris-ciliary body (ICB) upon ocular absorption by decreasing aqueous humor secretion, presumably by slowing the formation of bicarbonate ions and fluid flow, resulting in IOP reduction.

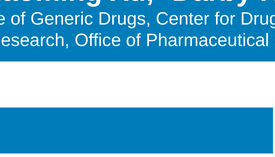

Figure 1. Pathogenesis of Intraocular Pressure.
Adapted from https://www.brightfocus.org/glaucoma/

Upon topical instillation, brinzolamide drug particles undergo dissolution in the tear fluid, which is partially governed by the drug's PSD, and dissolved brinzolamide becomes available for corneal and non-corneal absorption.

The residence time of the drug product on the surface of the eye, impacted by the product's apparent viscosity, influences the timeframe in which the drug is available for ocular absorption. Therefore, understanding the relationship between CQAs of these ophthalmic suspensions, such as apparent viscosity and PSD, and their pharmacokinetic and pharmacodynamic performance is critical in furtherance of safe and effective generic products for the treatment of IOP.

Materials and Methods

Test Articles: Reference Listed Drug (RLD), AZOPT (brinzolamide ophthalmic suspension 1%, NDA 020816), and five compositionally-equivalent test formulations (BRZ_001 to _005) intentionally manufactured to yield suspensions with varying PSD and apparent viscosities.

Physicochemical Characterization: PSD of brinzolamide was determined by laser diffraction on a MasterSizer 3000 (Malvern). Rheological properties were evaluated using a hybrid rheometer (TA Instrument) at 20°C.

***In Vivo* Study Design:** Multi-dose, parallel study with once-daily topical ophthalmic instillations of brinzolamide ophthalmic suspensions (0.5 mg/eye) for up to 14 days in New Zealand White (NZW) rabbits.

Pharmacodynamic Measurements: IOP measurements via applanation tonometer (Reichter Model 30TM), at the same time of day, for 5 days prior to dosing (acclimation) and on Days 1, 3, 5, 7, 9, 11, and 14 pre-dosing, and 0.25, 0.5, 1, 4, and 8 hours post-dosing each day (n=3).

Pharmacokinetic Measurements: Animals were euthanized on Days 7 and 14 at 0.25, 0.5, 1, 2, 4, and 8 hours, and relevant ocular tissues were quantified for brinzolamide (n=2). Pharmacokinetic parameters were determined with Phoenix WinNonlin 8.0 (non-compartmental model).

Results and Discussion (1/2)

Brinzolamide ophthalmic suspensions yielding variable physicochemical properties were prepared in-house and characterized, along with the reference comparator AZOPT, for PSD and apparent viscosity. Meaningful differences in both CQAs are noted, above and below target values measured for the comparator AZOPT (Table 1).

Table 1. CQAs of brinzolamide ophthalmic suspensions (mean ± standard deviation).

Formulation	Particle Size D[4,3] (µm) n=5	Apparent Viscosity (mPa·s) n=3
RLD AZOPT	2.84 ± 0.05	1123.6 ± 149.2
BRZ_001	1.59 ± 0.10	2293.9 ± 82.4
BRZ_002	4.76 ± 0.07	1359.1 ± 11.6
BRZ_003	10.20 ± 0.20	963.4 ± 193.0
BRZ_004	4.72 ± 0.05	170.2 ± 34.6
BRZ_005	5.13 ± 0.03	3326.0 ± 350.1

Pharmacodynamics: All formulations consistently showed the largest percent decrease in IOP within 1 hour on all measured days (Figure 2). While pointed differences were observed, they could not be correlated with the formulation characteristics assessed in this study. At 1 h of Day 14, BRZ_002 and BRZ_005, both with similar particle size but ranging in viscosity from average to the highest, respectively, showed the highest reduction of IOP relative to baseline. BRZ_001, with the smallest particle size but second to highest viscosity, showed similar IOP reduction as BRZ_003, with the largest particle size and average viscosity. The lack of significant pharmacodynamic differences may be attributed to the lack of substantial accumulation of drug in the target compartments [aqueous humor (AH) and ICB] under the dosing regimen evaluated.

Results and Discussion (2/2)

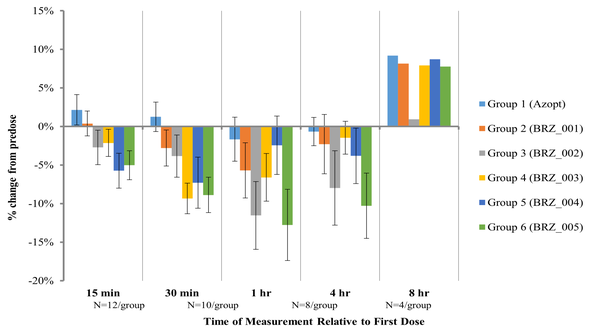

Figure 2. Mean IOP change from baseline for all groups at Day 14 of once-daily dosing of brinzolamide ophthalmic suspension to NZW rabbits (mean ± standard deviation).

Pharmacokinetics: The ocular concentrations *versus* time profiles of all the formulations did not show significant differences in AH and ICB compartments (Figure 3). Ocular exposure for AZOPT and BRZ_001 (lowest PS, second highest viscosity) appeared to be consistently higher than BRZ_004 (average PS, lowest viscosity) and BRZ_005 (average PS, highest viscosity) in cornea on Day 14, likely due to a confounded effect of PS reduction and viscosity increase on formulation retention and drug absorption. No other trends were noted in relevant ocular tissues.

Non-compartmental analysis showed no significant differences between the formulations in the AH and ICB compartments (Table 2). These results are consistent with the pharmacodynamic observations under the same dosing regimen, which did not show substantial impact of CQAs on PK/PD of brinzolamide ophthalmic suspensions under once-daily dosing regimen.

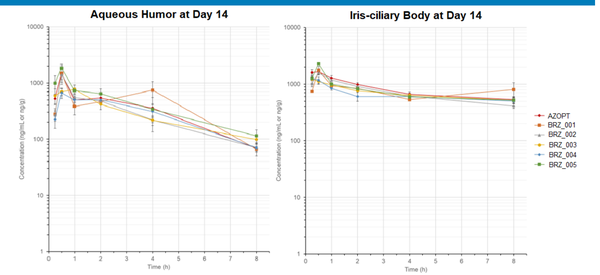

Figure 3. Mean brinzolamide concentration *versus* time in AH and ICB for all groups at Day 14 of once-daily dosing of brinzolamide ophthalmic suspensions to NZW rabbits (mean ± standard deviation; n=2/group/time-point).

Table 2. Non-compartmental analysis at Day 14 of once-daily dosing of brinzolamide ophthalmic suspensions to NZW rabbits.

Compartment	Parameter	AZOPT	BRZ_001	BRZ_002	BRZ_003	BRZ_004	BRZ_005
Aqueous Humor	AUC_{last} (h*ng/L)	2862.89	3420.93	2406.60	2395.16	2375.29	3542.85
	AUC_{inf} (h*ng/L)	3060.23	3693.54	2639.91	2768.89	2618.17	3913.55
	C_{max} (ng/L)	1449.50	1488.75	1417.00	733.25	666.50	1830.00
	T_{max} (h)	0.5	0.5	0.5	1.0	0.5	0.5
	$t_{1/2}$ (h)	2.00	2.84	2.29	2.63	2.39	2.24
Iris-ciliary body	AUC_{last} (h*ng/L)	6452.47	5974.52	5707.75	5509.31	5072.36	5932.09
	AUC_{inf} (h*ng/L)	10025.24	21457.71	8437.17	10396.62	9788.19	9380.14
	C_{max} (ng/L)	1660.50	1757.25	1590.75	1221.08	1253.25	2297.25
	T_{max} (h)	0.5	0.5	0.5	0.25	0.25	0.5
	$t_{1/2}$ (h)	4.65	13.30	4.57	6.56	6.51	4.59

Conclusion

Ophthalmic suspensions varying in PSD and apparent viscosity did not lead to remarkable differences in PK/PD of brinzolamide under once daily dosing regimen. Minor differences in exposure were observed in the cornea and conjunctiva compartments. These differences were less apparent in the ICB and AH compartments. IOP differences could not be clearly correlated to CQA differences. These observations could be attributed to the sparser dosing regimen assessed for brinzolamide ophthalmic suspension in this study, likely hindering drug concentration build-up in ocular tissues and leading to confounded observations. This study highlights current challenges in assessing drug product performance equivalence for brinzolamide ophthalmic suspensions.

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