Eye (2007) 00, 1–4

www.nature.com/eye

REVIEW

Predictive value of the efficacy of glaucoma medications in regulatory trials: Phase I–III to post-marketing studies

WC Stewart[1,2,3] and JN Jenkins[1,2]

Abstract

Purpose **To determine the predictive value of early Phase trials (I–II) for the ocular hypotensive efficacy observed in Phases III and IV.**

Design **A review of published literature.**

Methods **This study evaluated 12 medicines in 65 articles in the literature with at least two phases available.**

Results **For medicines with Phase I results available ($n=3$), the average reduction in intraocular pressure (IOP) from untreated baseline was 16%, 26% for Phase II, 26% for Phase III, and 24% for Phase IV. For medicines with Phase II results available ($n=6$), the average reduction in IOP was 23%, 24% for Phase III, and 23% for Phase IV. For medicines with Phase III results available ($n=11$), the average reduction in IOP was 25 and 24% for Phase IV.**

Conclusion **This study indicates that early phase trials usually approximated the results of later regulatory studies and post-commercialization trials.**

Eye (2007) **0,** 000–000. doi:10.1038/sj.eye.6702913

Keywords: glaucoma medications; phase I–IV; intraocular pressure; ocular hypotensive efficacy

Introduction

To gain regulatory approval for a new medicine, a pharmaceutical company must take the new product through a series of clinical trials (Phases I–III). A Phase I trial represents the first instance a new product is used in human subjects and is performed primarily to collect safety information. In a Phase II trial, a new product is used for the first time in patients with the target disease to gain dosing and concentration information. At least two Phase III trials are performed and they are expanded in size and duration. These trials typically provide the most information on the efficacy and safety of the new product on which regulatory approval is based. Phase IV studies are those that are performed after commercial release of the medicine.

A pharmaceutical company must make a decision at the end of each phase whether the efficacy and safety information warrants the resources, in money and personnel, to continue clinical development. Consequently, adequately performed early trials (I–II) should predict the results of Phase III and IV studies. However, the limited size and duration, as well as the subject selection, might restrict the early phase trial's ability to accurately predict future results. Unfortunately, little information is available regarding how well Phase I–III trials predict the ultimate commercial efficacy of a new product.

Methods

Using published literature on Pubmed (http://www.ncbi.nlm.nih.gov/entrez/query), we evaluated the Phase I–III trials for glaucoma medicines that became commercially available since 1977, and at least the first five Phase IV trials available. We used the generic and brand name of each included medicine as keywords along with the term 'glaucoma'. We wished to determine the predictive value of early Phase

[1]PRN Pharmaceutical Research Network, LLC, Dallas, TX, USA

[2]Carolina Eye Institute, University of South Carolina, School of Medicine, Columbia, SC, USA

Correspondence: WC Stewart, Department of Ophthalmology, PRN Pharmaceutical Research Network, LLC, 1 Southpark Circle, Suite 110, Charleston, SC 29407, USA
Tel: +1 843 762 6500; Fax: +1 843 762 7444.
E-mail: info@prnorb.com

[3]Dr WC Stewart works as an independent glaucoma researcher and lecturer and receives grants and honoraria from multiple companies. This study was not supported by any public or private funding agency.

Received: 24 February 2007
Accepted in revised form: 25 May 2007

Journal: EYE ☐ Disk used Despatch Date: 4/6/2007 Ed: Anjana
Article: npg.eye.6702913 Pages: 1--4 Op:NP TemplateVer.: 1.0.4

Table 1 Mean reductions from untreated baselines for the medicines included in this review

	Phase I		*Phase II*		*Phase III*		*Phase IV*	
Medicine	N	%	N	%	N	%	N	%
Apraclonidine[1,2]			2	16.5	1	15.8		
Betaxolol[3–8]					1	13.2	3	18.6
Bimatoprost[9–14]					1	32.4	5	32.1
Brimonidine[15–23]			1	22.8	1	22.8	3	21.1
Dorzolamide/timolol fixed combination[24–28]					1	29.4	2	28.2
Dorzolamide[29–32]			3	16.9			2	17.4
Latanoprost/timolol fixed combination[15,24,33,34]					1	33.3	3	27.7
Latanoprost[9,12,16,17,25,26,29,35–55]	1	30.7	5	25.9	3	27.8	17	27.5
Timolol gel-forming solution[12,38,56,57]					2	21.8	2	16.5
Timolol[1,3,8,10,11,13,15,18–21,28,31,34–37,44,49,52,55,56,58,59–65]	1	23.8	3	34.2	5	26.6	17	22.2
Travoprost[44]					2	26.9	1	30.7
Unoprostone[39–43]	2	5.4	2	15.8	1	18.2	5	15.4

trials (I–II) for the ocular hypotensive efficacy observed in Phases III and IV.

This study evaluated 12 medicines in 65 articles in the literature with at least two phases available (see Table 1).[1–65]

Results

For medicines with Phase I results available ($n=3$), the average reduction in intraocular pressure from untreated baseline was 16%, 26% for Phase II, 26% for Phase III, and 24% for Phase IV. For medicines with Phase II results available ($n=6$), the average reduction in intraocular pressure was 23%, 24% for Phase III, and 23% for Phase IV. For medicines with Phase III results available ($n=11$), the average reduction in intraocular pressure was 25%, and it was 24% for Phase IV. For medicines with the earliest results available in Phase I, II, or III, all products were within 10, 12, and 6%, respectively, of Phase IV study efficacy.

Discussion

The results of this review indicate that early phase trials usually approximated the results of later regulatory studies and post-commercialization trials. However, caution is warranted because results still deviated between phases by clinically important amounts in several studies. This was especially apparent with timolol, which demonstrated reduced efficacy over a large number of Phase IV trials compared to earlier phase studies. The reason for this decrease was apparent by our results.

Nonetheless, the results of this review should give a pharmaceutical company, and the associated investigators, some confidence that a glaucoma medicine effective in early regulatory trials will probably have similar efficacy in the subsequent phases and after commercialization.

However, the results of this study are limited in that it reviewed only products launched commercially. Data and the predictive values of their regulatory trials were not available for the products that failed development. More research is needed, in general, with clinical measures and the development process, to help investigators and pharmaceutical companies know how to most efficiently develop a new glaucoma product.

References

1 Nagasubramanian S, Hitchings RA, Demailly P, Chuniaud M, Pannarale MR, Pecori-Giraldi J *et al* Comparision of apraclonidine and timolol in chronic open-angle glaucoma. A three-month study. *Ophthalmology* 1993; **100**(9): 1318–1323.
2 Abrams DA, Robin AL, Pollack IP, deFaller JM, DeSantis L. The safety and efficacy of topical 1% ALO 2145 (*p*-aminoclonidine hydrochloride) in normal volunteers. *Arch Ophthalmol* 1987; **105**(9): 1205–1207.
3 Strahlman E, Tipping R, Vogel R. A double-masked, randomized 1-year study comparing dorzolamide (Trusopt), timolol, and betaxolol. International Dorzolamide Study Group. *Arch Ophthalmol* 1995; **113**(8): 1009–1016.
4 Berry Jr DP, Van Buskirk EM, Shields MB. Betaxolol and timolol. A comparison of efficacy and side effects. *Arch Ophthalmol* 1984; **102**(1): 42–45.
5 Weinreb RN, Caldwell DR, Goode SM, Horwitz BL, Laibovitz R, Shrader CE *et al* A double-masked three-month comparison between 0.25% betaxolol suspension and 0.5% betaxolol ophthalmic solution. *Am J Ophthalmol* 1990; **110**(2): 189–192.
6 Feghali JG, Kaufman PL. Decreased intraocular pressure in the hypertensive human eye with betaxolol, a beta 1-adrenergic antagonist. *Am J Ophthalmol* 1985; **100**(6): 777–782.
7 Caldwell DR, Salisbury CR, Guzek JP. Effects of topical betaxolol in ocular hypertensive patients. *Arch Ophthalmol* 1984; **102**(4): 539–540.

8 Feghali JG, Kaufman PL, Radius RL, Mandell AI. A comparison of betaxolol and timolol in open angle glaucoma and ocular hypertension. *Acta Ophthalmol (Copenh)* 1988; **66**(2): 180–186.
9 DuBiner H, Cooke D, Dirks M, Stewart WC, VanDenburgh AM, Felix C. Efficacy and safety of bimatoprost in patients with elevated intraocular pressure: a 30-day comparison with latanoprost. *Surv Ophthalmol* 2001; **45**(Suppl 4): S353–S360.
10 Sherwood M, Brandt J, Bimatoprost Study Groups 1 and 2. Six-month comparison of bimatoprost once-daily and twice-daily with timolol twice-daily in patients with elevated intraocular pressure. *Surv Ophthalmol* 2001; **45**(Suppl 4): S361–S368.
11 Cohen JS, Gross RL, Cheetham JK, VanDenburgh AM, Bernstein P, Whitcup SM. Two-year double-masked comparison of bimatoprost with timolol in patients with glaucoma or ocular hypertension. *Surv Ophthalmol* 2004; **49**(Suppl 1): S45–S52.
12 Walters TR, DuBiner HB, Carpenter SP, Khan B, VanDenburgh AM, Bimatoprost Circadian IOP Study Group. 24-H IOP control with once-daily bimatoprost, timolol gel-forming solution, or latanoprost: a 1-month, randomized, comparative clinical trial. *Surv Ophthalmol* 2004; **49**(Suppl 1): S26–S35.
13 Laibovitz RA, VanDenburgh AM, Felix C, David R, Batoosingh A, Rosenthal A *et al* Comparison of the ocular hypotensive lipid AGN 192024 with timolol: dosing, efficacy, and safety evaluation of a novel compound for glaucoma management. *Arch Ophthalmol* 2001; **119**(7): 994–1000.
14 Brubaker RF, Schoff EO, Nau CB, Carpenter SP, Chen K, Vandenburgh AM. Effects of AGN 192024, a new ocular hypotensive agent, on aqueous dynamics. *Am J Ophthalmol* 2001; **131**(1): 19–24.
15 Stewart WC, Stewart JA, Day D, Sharpe ED. Efficacy and safety of timolol maleate/latanoprost fixed combination *versus* timolol maleate and brimonidine given twice daily. *Acta Ophthalmol Scand* 2003; **81**(3): 242–246.
16 Liu CJ, Ko YC, Cheng CY, Chiu AW, Chou JC, Hsu WM *et al* Changes in intraocular pressure and ocular perfusion pressure after latanoprost 0.005% or brimonidine tartrate 0.2% in normal-tension glaucoma patients. *Ophthalmology* 2002; **109**(12): 2241–2247.
17 Kampik A, Arias-Puente A, O'Brart DP, Vuori ML, European Latanoprost Study Group. Intraocular pressure-lowering effects of latanoprost and brimonidine therapy in patients with open-angle glaucoma or ocular hypertension: a randomized observer-masked multicenter study. *J Glaucoma* 2002; **11**(2): 90–96.
18 Konstas AG, Stewart WC, Topouzis F, Tersis I, Holmes KT, Stangos NT. Brimonidine 0.2% given two or three times daily *versus* timolol maleate 0.5% in primary open-angle glaucoma. *Am J Ophthalmol* 2001; **131**(6): 729–733.
19 Schuman JS. Clinical experience with brimonidine 0.2% and timolol 0.5% in glaucoma and ocular hypertension. *Surv Ophthalmol* 1996; **41**(Suppl 1): S27–S37.
20 LeBlanc RP. Twelve-month results of an ongoing randomized trial comparing brimonidine tartrate 0.2% and timolol 0.5% given twice daily in patients with glaucoma or ocular hypertension. Brimonidine Study Group 2. *Ophthalmology* 1998; **105**(10): 1960–1967.
21 Katz LJ. Brimonidine tartrate 0.2% twice daily *vs* timolol 0.5% twice daily: 1-year results in glaucoma patients. Brimonidine Study Group. *Am J Ophthalmol* 1999; **127**(1): 20–26.
22 Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K. A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. *Arch Ophthalmol* 1997; **115**(7): 847–852.
23 Derick RJ, Robin AL, Walters TR, Barnebey HS, Choplin N, Schuman J *et al* Brimonidine tartrate: a one-month dose response study. *Ophthalmology* 1997; **104**(1): 131–136.
24 Shin DH, Feldman RM, Sheu WP, Fixed Combination Latanoprost/Timolol Study Group. Efficacy and safety of the fixed combinations latanoprost/timolol *versus* dorzolamide/timolol in patients with elevated intraocular pressure. *Ophthalmology* 2004; **111**(2): 276–282.
25 Konstas AG, Papapanos P, Tersis I, Houliara D, Stewart WC. Twenty-four-hour diurnal curve comparison of commercially available latanoprost 0.005% *versus* the timolol and dorzolamide fixed combination. *Ophthalmology* 2003; **110**(7): 1357–1360.
26 Konstas AG, Papapanos P, Tersis I, Houliara D, Stewart WC. Twenty-four-hour diurnal curve comparison of commercially available latanoprost 0.005% *versus* the timolol and dorzolamide fixed combination. *Ophthalmology* 2003; **110**(7): 1357–1360.
27 Strohmaier K, Snyder E, DuBiner H, Adamsons I. The efficacy and safety of the dorzolamide–timolol combination *versus* the concomitant administration of its components. Dorzolamide–Timolol Study Group. *Ophthalmology* 1998; **105**(10): 1936–1944.
28 Clineschmidt CM, Williams RD, Snyder E, Adamsons IA. A randomized trial in patients inadequately controlled with timolol alone comparing the dorzolamide-timolol combination to monotherapy with timolol or dorzolamide. Dorzolamide–Timolol Combination Study Group. *Ophthalmology* 1998; **105**(10): 1952–1959.
29 O'Donoghue EP. A comparison of latanoprost and dorzolamide in patients with glaucoma and ocular hypertension: a 3 month, randomised study. Ireland Latanoprost Study Group. *Br J Ophthalmol* 2000; **84**(6): 579–582.
30 Lippa EA, Carlson LE, Ehinger B, Eriksson LO, Finnstrom K, Holmin C *et al* Dose response and duration of action of dorzolamide, a topical carbonic anhydrase inhibitor. *Arch Ophthalmol* 1992; **110**(4): 495–499.
31 Heijl A, Strahlman E, Sverrisson T, Brinchman-Hansen O, Puustjarvi T, Tipping R. A comparison of dorzolamide and timolol in patients with pseudoexfoliation and glaucoma or ocular hypertension. *Ophthalmology* 1997; **104**(1): 137–142.
32 Kitazawa Y, Azuma I, Iwata K, Tsukahara S, Shiose Y, Araie M *et al* Dorzolamide, a topical carbonic anhydrase inhibitor: a two-week dose-response study in patients with glaucoma or ocular hypertension. *J Glaucoma* 1994; **3**: 275–279.
33 Higginbotham EJ, Feldman R, Stiles M, Dubiner H, Fixed Combination Investigative Group. Latanoprost and timolol combination therapy *vs* monotherapy: one-year randomized trial. *Arch Ophthalmol* 2002; **120**(7): 915–922.
34 Larsson LI. Effect on intraocular pressure during 24 h after repeated administration of the fixed combination of latanoprost 0.005% and timolol 0.5% in patients with ocular hypertension. *J Glaucoma* 2001; **10**(2): 109–114.
35 Watson P, Stjernschantz J. A six-month, randomized, double-masked study comparing latanoprost with timolol in open-angle glaucoma and ocular hypertension.

The Latanoprost Study Group. *Ophthalmology* 1996; **103**(1): 126–137.
36 Camras CB. Comparison of latanoprost and timolol in patients with ocular hypertension and glaucoma: a six-month masked, multicenter trial in the United States. The United States Latanoprost Study Group. *Ophthalmology* 1996; **103**(1): 138–147.
37 Hedman K, Larsson LI. The effect of latanoprost compared with timolol in African-American, Asian, Caucasian, and Mexican open-angle glaucoma or ocular hypertensive patients. *Surv Ophthalmol* 2002; **47**(Suppl 1): S77–S89.
38 Sponsel WE, Mensah J, Kiel JW, Remky A, Trigo Y, Baca W *et al* Effects of latanoprost and timolol-XE on hydrodynamics in the normal eye. *Am J Ophthalmol* 2000; **130**(2): 151–159.
39 Sponsel WE, Paris G, Trigo Y, Pena M. Comparative effects of latanoprost (Xalatan) and unoprostone (Rescula) in patients with open-angle glaucoma and suspected glaucoma. *Am J Ophthalmol* 2002; **134**(4): 552–559.
40 Tsukamoto H, Mishima HK, Kitazawa Y, Araie M, Abe H, Negi A, Glaucoma Study Group. A comparative clinical study of latanoprost and isopropyl unoprostone in Japanese patients with primary open-angle glaucoma and ocular hypertension. *J Glaucoma* 2002; **11**(6): 497–501.
41 Kobayashi H, Kobayashi K, Okinami S. A comparison of intraocular pressure-lowering effect of prostaglandin F2 - alpha analogues, latanoprost, and unoprostone isopropyl. *J Glaucoma* 2001; **10**(6): 487–492.
42 Aung T, Chew PT, Yip CC, Chan YH, See JL, Khng CG *et al* A randomized double-masked crossover study comparing latanoprost 0.005% with unoprostone 0.12% in patients with primary open-angle glaucoma and ocular hypertension. *Am J Ophthalmol* 2001; **131**(5): 636–642.
43 Saito M, Takano R, Shirato S. Effects of latanoprost and unoprostone when used alone or in combination for open-angle glaucoma. *Am J Ophthalmol* 2001; **132**(4): 485–489.
44 Netland PA, Landry T, Sullivan EK, Andrew R, Silver L, Weiner A *et al* Travoprost compared with latanoprost and timolol in patients with open-angle glaucoma or ocular hypertension. *Am J Ophthalmol* 2001; **132**(4): 472–484.
45 Nagasubramanian S, Sheth GP, Hitchings RA, Stjernschantz J. Intraocular pressure-reducing effect of PhXA41 in ocular hypertension. Comparison of dose regimens. *Ophthalmology* 1993; **100**(9): 1305–1311.
46 Alm A, Villumsen J. PhXA34, a new potent ocular hypotensive drug. A study on dose-response relationship and on aqueous humor dynamics in healthy volunteers. *Arch Ophthalmol* 1991; **109**(11): 1564–1568.
47 Villumsen J, Alm A. PhXA34−a prostaglandin F2 alpha analogue. Effect on intraocular pressure in patients with ocular hypertension. *Br J Ophthalmol* 1992; **76**(4): 214–217.
48 Alm A, Villumsen J, Tornquist P, Mandahl A, Airaksinen J, Tuulonen A *et al* Intraocular pressure-reducing effect of PhXA41 in patients with increased eye pressure. A one-month study. *Ophthalmology* 1993; **100**(9): 1312–1316 discussion 1316–1317.
49 Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian Latanoprost Study Group. *Ophthalmology* 1995; **102**(12): 1743–1752.
50 Racz P, Ruzsonyi MR, Nagy ZT, Bito LZ. Maintained intraocular pressure reduction with once-a-day application of a new prostaglandin F2 alpha analogue (PhXA41). An in-hospital, placebo-controlled study. *Arch Ophthalmol* 1993; **111**(5): 657–661.
51 Larsson LI, Mishima HK, Takamatsu M, Orzalesi N, Rossetti L. The effect of latanoprost on circadian intraocular pressure. *Surv Ophthalmol* 2002; **47**(Suppl 1): S90–S96.
52 Camras CB, Wax MB, Ritch R, Weinreb R, Robin AL, Higginbotham EJ *et al* Latanoprost treatment for glaucoma: effects of treating for 1 year and of switching from timolol. United States Latanoprost Study Group. *Am J Ophthalmol* 1998; **126**(3): 390–399.
53 Watson PG. Latanoprost. Two years' experience of its use in the United Kingdom. Latanoprost Study Group. *Ophthalmology* 1998; **105**(1): 82–87.
54 Rulo AH, Greve EL, Geijssen HC, Hoyng PF. Reduction of intraocular pressure with treatment of latanoprost once daily in patients with normal-pressure glaucoma. *Ophthalmology* 1996; **103**(8): 1276–1282.
55 Mishima HK, Masuda K, Kitazawa Y, Azuma I, Araie M. A comparison of latanoprost and timolol in primary open-angle glaucoma and ocular hypertension. A 12-week study. *Arch Ophthalmol* 1996; **114**(8): 929–932.
56 Stewart WC, Leland TM, Cate EA, Stewart JA. Efficacy and safety of timolol solution once daily *versus* timolol gel in treating elevated intraocular pressure. *J Glaucoma* 1998; **7**(6): 402–407.
57 Schenker HI, Silver LH. Long-term intraocular pressure-lowering efficacy and safety of timolol maleate gel-forming solution 0.5% compared with Timoptic XE 0.5% in a 12-month study. *Am J Ophthalmol* 2000; **130**(2): 145–150.
58 Stewart RH, Kimbrough RL, Ward RL. Betaxolol *vs* timolol. A six-month double-blind comparison. *Arch Ophthalmol* 1986; **104**(1): 46–48.
59 Zimmerman TJ, Kass MA, Yablonski ME, Becker B. Timolol maleate: efficacy and safety. *Arch Ophthalmol* 1979; **97**(4): 656–658.
60 Zimmerman TJ, Kaufman HE. Timolol. A beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol* 1977; **95**(4): 601–604.
61 Katz IM, Hubbard WA, Getson AJ, Gould AL. Intraocular pressure decrease in normal volunteers following timolol ophthalmic solution. *Invest Ophthalmol* 1976; **15**(6): 489–492.
62 LeBlanc RP, Saheb NE, Krip G. Timolol: long-term Canadian multicentre study. *Can J Ophthalmol* 1985; **20**(4): 128–130.
63 Stewart WC, Stewart JA, Holmes KT, Leech JN. Differences in ocular surface irritation between timolol hemihydrate and timolol maleate. *Am J Ophthalmol* 2000; **130**(6): 712–716.
64 Sakurai M, Araie M, Oshika T, Mori M, Masuda K, Ueno R *et al* Effects of topical application of UF-021, a novel prostaglandin derivative, on aqueous humor dynamics in normal human eyes. *Jpn J Ophthalmol* 1991; **35**(2): 156–165 erratum in *Jpn J Ophthalmol* 1992;**36**(4):491.
65 Azuma I, Masuda K, Kitazawa Y, Takase M, Yamamura H. Double-masked comparative study of UF-021 and timolol ophthalmic solutions in patients with primary open-angle glaucoma or ocular hypertension. *Jpn J Ophthalmol* 1993; **37**(4): 514–525.