

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

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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.

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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

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

Medicine	Phase I		Phase II		Phase III		Phase IV	
	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 not 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.

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