Provisional Translation (as of January 2026)*

Principles on Development of Combination Ophthalmic Solutions for Glaucoma (Early Consideration)

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1. Introduction

Glaucoma is a progressive optic neuropathy characterized by damage to the optic nerve. In Japan, it is known that more than 5% of patients aged 40 years or older suffer from glaucoma, and the disease is one of the leading causes of visual impairment[1].

The only evidence-based, reliable treatment for glaucoma is considered to be intraocular pressure-lowering therapy, for which ophthalmic solutions are mainly used[2]. For the treatment of glaucoma, multiple ophthalmic solutions with different mechanisms of action have been approved for marketing. In "The Japan Glaucoma Society Guidelines for Glaucoma (5th Edition)" summarized by the Glaucoma Guideline Preparation Committee of the Japan Glaucoma Society, ophthalmic solutions are classified into two categories "first-line drugs" and "second-line drugs" based on their mechanisms of action, and a general policy for the introduction of ophthalmic solutions is presented.

If it is not possible to achieve the target intraocular pressure reduction or adequately control the progression of visual field disorder with single-active ingredient drugs containing one active ingredient, multi-drug combination therapy is selected. However, since decreased medication adherence associated with an increase in the number of ophthalmic solutions and the frequency of ocular instillation greatly affects the success or failure of intraocular pressure-lowering therapy, it is deemed necessary to consider the use of combination ophthalmic solutions containing multiple active ingredients when multiple drugs are concomitantly used in order to improve adherence[2].

In Japan, multiple combination ophthalmic solutions, which combine two active ingredients from first- or second-line drugs, have already been marketed.

The purpose of this Early Consideration is to present points to consider, etc. when planning confirmatory studies to be conducted during the development of combination ophthalmic solutions for glaucoma containing only approved active ingredients for the treatment of glaucoma and ocular hypertension in Japan. It should be noted that these considerations are based on currently available

* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

knowledge and may change as new findings emerge. In addition, the following mainly presents the concept of confirmatory studies of combination ophthalmic solutions containing two active ingredients. For the development of combination ophthalmic solutions that combine three or more active ingredients, the sponsors should consult with PMDA.

2. Confirmatory study

2.1 General matters

Efficacy should be evaluated in a randomized, parallel-group study with an appropriate comparator group designed to confirm superiority over the comparator.

2.2 Comparator

In the case of combination ophthalmic solutions containing two active ingredients of first-line drugs or two active ingredients from second-line drugs, the sponsor should use each single-active ingredient of the active ingredients contained in the combination as the comparators. In the case of combination ophthalmic solutions in which the active ingredients of a first-line drug and a second-line drug are combined, the sponsor should use only the first-line drug as the comparator, because it is unlikely to switch to the combination ophthalmic solution to add the first-line drug to patients who have not responded sufficiently to the second-line drug.

2.3 Target patient

The target patients are those with glaucoma or ocular hypertension who have not responded sufficiently to the comparator (single-active ingredient drug containing the active ingredient). However, in the case of combination ophthalmic solutions that combine the active ingredients of a first-line drug and a second-line drug, the study population should be limited to patients with an insufficient response to the first-line drug. This is because it is unlikely to switch to the combination ophthalmic solution to add the first-line drug to patients who have not responded sufficiently to the second-line drug as described above. If the confirmatory study includes patients who have not responded sufficiently to a different active ingredient with a mechanism of action generally similar to that of each active ingredient of the combination ophthalmic solution to be developed, the sponsors should consult with PMDA.

In selecting the target patient, an inadequate response to the comparator is roughly defined as having an intraocular pressure of 18 mmHg or higher when the comparator, a single-active ingredient drug, is instilled for a certain period of time (at least 4 weeks).

2.4 Primary endpoint

Since the only evidence-based, reliable treatment for glaucoma is considered to be intraocular

pressure-lowering therapy, the primary endpoint should be the change in intraocular pressure from baseline[2)].

For time point of intraocular pressure evaluation (time of measurement), appropriate time points (time at which the intraocular pressure-lowering effect reaches its peak, etc.) should be determined based on the intraocular pressure-lowering profile of each active ingredient contained. If the intraocular pressure-lowering profile (time at which the intraocular pressure-lowering effect of each active ingredient contained reaches its peak) is different, the primary endpoint should be mean change in intraocular pressure measurements (mean intraocular pressure change) at multiple time points deemed be appropriate based on the profile.

Intraocular pressure is known to have diurnal variation[2)]. Therefore, even if the change in intraocular pressure at a single measurement time point is set as the primary endpoint in light of the concerned variation, intraocular pressure at multiple time points throughout the day including the time point immediately before instillation so that the persistence of the intraocular pressure-lowering effect throughout the day should be investigated as a secondary endpoint or exploratory endpoint.

2.5 Treatment duration/evaluation period

The primary evaluation time point should be set at a time point at which it is at least possible to confirm that the intraocular pressure-lowering effect reaches its plateau based on the results of clinical studies. of single-active ingredient drugs.

2.6 Masking

In order to minimize bias by subjects, investigators, etc., the confirmatory studies should, in principle, be conducted in a double-masking manner. If double-masking is not feasible, single-masking (assessor-masked) is acceptable, however, in such a case, appropriate measures should be taken to warrant the masking as far as possible, such as following:

- When the test drug and comparator differ in appearance, each product should be packaged in identical, indistinguishable containers or boxes.
- The investigator involved in evaluation will not confirm the information on the identification of the investigational product from subjects and will not be involved in the operations of supply and collection of the investigational product.

3. Other considerations

If it is difficult to evaluate the efficacy and safety of long-term concomitant administration of the individual active ingredients based on the results of post-marketing surveillance of single-active ingredient drug of each active ingredient contained in combination ophthalmic solutions, it may be necessary to conduct a long-term study of the ophthalmic solutions. In such cases, the sponsors should

consult with PMDA. When conducting a long-term administration study of combination ophthalmic solutions, ophthalmic solutions expected to be concomitantly used with the combination ophthalmic solution in clinical practice should be allowed for concomitant use, and it is desirable to collect safety information when the concomitant ophthalmic solution is used with the combination ophthalmic solution under development for the long term.

4. Reference

1) A nationwide survey of newly certified visually impaired individuals in Japan for the fiscal year 2019: impact of the revision of criteria for visual impairment certification. Jpn J Ophthalmol 2023; 67: 346-52
2) The Japan Glaucoma Society Guidelines for Glaucoma (5th Edition) Journal of Japanese Ophthalmological Society 2022; 126: 85-177
3) Current and emerging fixed combination therapies in glaucoma: a safety and tolerability review. Expert Opin Drug Saf 2020; 19: 1445-60