Development of Triptans in Japan: Bridging Strategy Based on the ICH-E5 Guideline

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In Japan, five new drug applications (NDAs) of triptans have been approved through a bridging strategy. They constituted the largest target disease field among 26 NDAs which had been approved through the strategy between 1999 and 2003. The bridging strategies of the drugs were classified into two major categories to be described below. One was to conduct a placebo-controlled dose-response study as a bridging study in an attempt to extrapolate the data from the pivotal foreign Phase III studies including a repeated dose study (*i.e.*, zolmitriptan, sumatriptan succinate, and eletriptan hydrobromide). Another was to conduct a placebo-controlled Phase III study in Japan in an attempt to extrapolate the data for efficacy from a repeated dose study (*i.e.*, sumatriptan and rizatriptan benzoate). The extrinsic ethnic factors relating to triptans did not interfere with the extrapolation of foreign clinical data in the five applications. A bridging strategy reduced the number of clinical trials and/or sample size. The accumulation of these bridging experiences indicated that foreign clinical data could be used to support the approval of triptans in Japan.

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INTRODUCTION

In the development of a new drug, a bridging strategy has been taken more frequently in Japan. A bridging strategy, that conducts a bridging study to allow the extrapolation of foreign clinical data to a new region, was authorized by a guideline of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH). The guideline, entitled "Ethnic factors in the acceptability of foreign clinical data"[1] and encoded as E5, was implemented officially in Japan on August 11, 1998.[2] To minimize the duplication of clinical data in two different regions, the guideline describes the factors which could lead to different responses in different ethnic groups and recommends that foreign clinical data be used to support approval if there is a bridging study in one region which demonstrates similarity in the other region.[3,4]

Triptans, $5HT_{1B/1D}$ receptor agonists, are medicines for migraine attack treatment. Six new drug applications (NDAs) of triptans have been approved under the Pharmaceutical Affairs Law of Japan between 2000 and 2003. The first approved application, which was related to sumatriptan succinate Injection and was approved on January 18, 2000, was based on clinical data obtained in Japan, while other five NDAs were approved through a bridging strategy (Table 1). These applicants adopted their own strategies which could be classified into two types.[3]

In this article, we analyzed the bridging strategies for triptans and examined how foreign clinical data were used in these applications.

MATERIALS AND METHODS

The information sources used for analyses in this study are the review reports prepared by the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Heath Sciences (the preceding organization of Pharmaceuticals and Medical Devices Agency) for each NDA and the summaries of the data submitted by applicants, both of which are publicly available at the Web site.[5]

Table 1. Triptans Approved in Japan Based on Bridging Strategy in Japan

	Application date	Approval date
Zolmitriptan	2000. 3. 13	2001. 6. 20
Sumatriptan succinate	2000. 8. 2	2001. 6. 20
Eletriptan hydrobromide	2000. 6. 30	2002. 4. 11
Sumatriptan	2001. 5. 30	2003. 4. 16
Rizatriptan benzoate	2001. 11. 30	2003. 7. 17

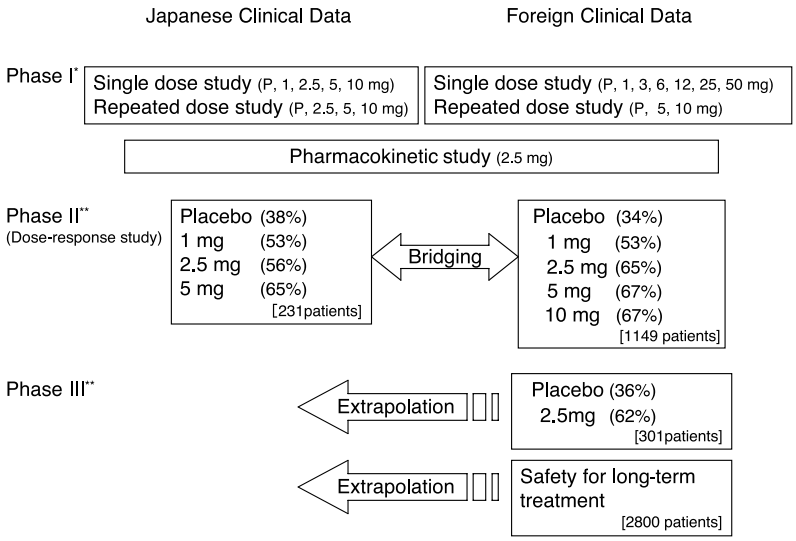

Fig. 1. Clinical Data Package of Zolmitriptan Tablets

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III; ( ): Headache relief rate within 2 hr after administration. [ ]: Number of patients who received the investigational drug.

We analyzed the information and illustrated clinical data packages of each application described in Figs. 1–7. Not all clinical trials are included in these applications; however, essential ones to compose the complete clinical data package, such as a bridging study, a counterpart study, and an extrapolated pivotal foreign study, are mentioned in the figures. They represent our views and do not necessarily represent the views of the regulatory authorities and applicants.

RESULTS

Zolmitriptan Tablets (Zomig® Tablets, Fig. 1)

The pharmacokinetic profile of zolmitriptan in the Japanese patient population was similar to that in the foreign counterpart. Initially, the Japanese dose-response study was not planned as a bridging study. After the guideline was established,[3] however, the applicant changed the study design to evaluate dose-dependency in a study including placebo group for comparable design to the foreign dose-response study. To compare the efficacy of zolmitriptan in the two populations, the headache relief rate within 2 hr after administration (primary endpoint) was adjusted for headache severity because the severity of initial headache affected headache relief. The bridging study demonstrated that dose response, efficacy, and safety in the Japanese study were comparable to those in the foreign counterpart, indicating that the foreign data were extrapolatable to Japan.

Sumatriptan Succinate Tablets (IMIGRAN® Tablets, Fig. 2)

The pharmacokinetic profiles were comparable between the Japanese and foreign patient populations. The first dose response study (placebo, 50, and 100 mg groups; not shown in Fig. 2) in Japan failed to indicate clear dose dependency in efficacy, and the recommended therapeutic dose was indeterminable. The applicant was required to conduct the dose response study again by using the definitive criteria for efficacy.

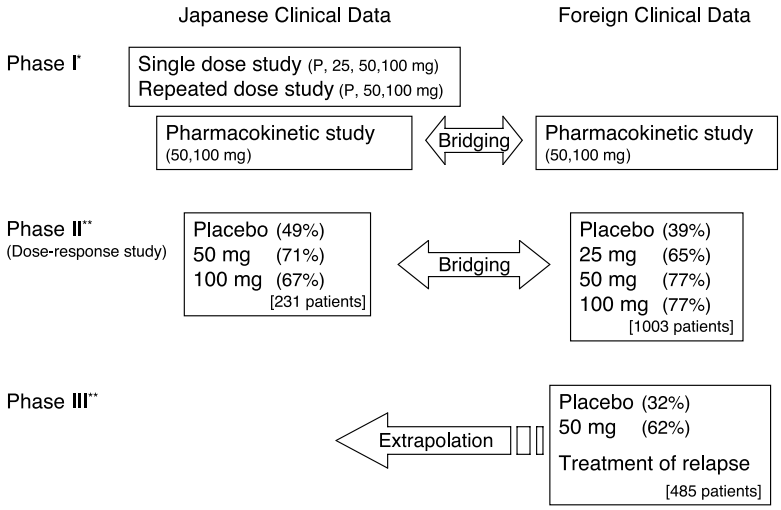

Fig. 2. Clinical Data Package of Sumatriptan Succinate Tablets

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III; ( ): Headache relief rate within 4 hr after administration. [ ]: Number of patients who received the investigational drug.

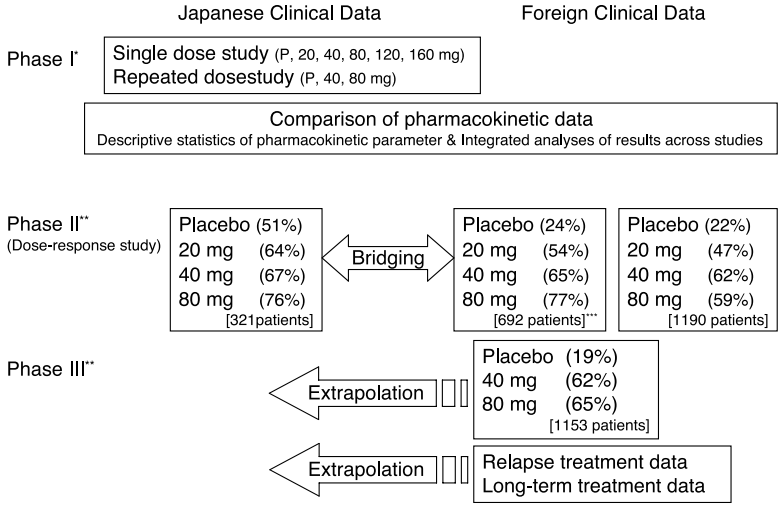

Fig. 3. Clinical Data Package of Eletriptan Hydrobromide Tablets

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III; ( ): Headache relief rate within 2 hr after administration. [ ]: Number of patients who received the investigational drug. ***: The sumatriptan group was included.

The second Japanese dose response study (placebo, 50, and 100 mg groups) was conducted as a bridging study by using the same efficacy evaluation criteria used in the counterpart study (placebo, 25, 50, and 100 mg groups). The headache relief rate within 4 hr after administration (primary endpoint), the time-course of headache relief rate, and the percentage of pain-free patients were used for efficacy comparison. In this case, dose response, efficacy, and safety were comparable between the two patient populations. Therefore, the data from the Phase III study (placebo, 50 mg, and relapse treatment groups) were extrapolatable to Japan.

Eletriptan Hydrobromide Tablets (RELPAX® Tablets, Fig. 3)

Regarding pharmacokinetic profiles, the maximum plasma concentration and AUC at single oral doses (10–40 mg) were significantly lower (by approximately 30–40%) in the Japanese than foreign patient population.

The Japanese dose-response study, that was originally planed as a bridging study, showed dose dependency for primary endpoint (headache relief

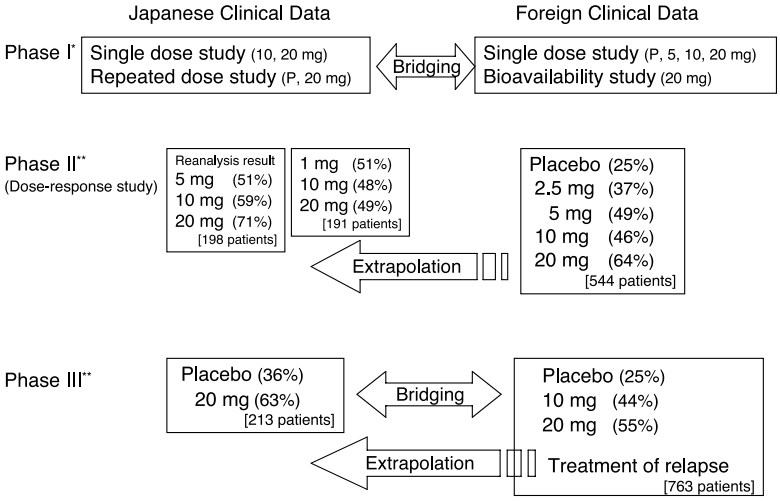

Fig. 4. Clinical Data Package of Sumatriptan Nasal Spray (Application)

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III; ( ): Headache relief rate within 2 hr after administration. [ ]: Number of patients who received the investigational drug.

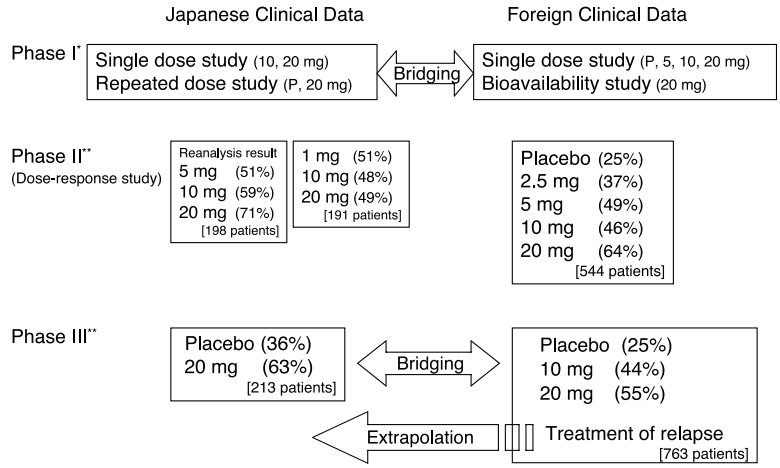

Fig. 5. Clinical Data Package of Sumatriptan Nasal Spray (Approval)

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III; ( ): Headache relief rate within 2 hr after administration. [ ]: Number of patients who received the investigational drug.

rate within 2 hr after administration) and revealed dose-dependent adverse events. At a dose of 80 mg, the incidence of adverse events, such as nausea and somnolence, was significantly higher in the Japanese than foreign patient population (nausea, 10.4 *versus* 5.7%; somnolence, 16.9 *versus* 6.6%).

In this case, the bridging study showed that dose dependency for efficacy was comparable but safety profiles were different between the Japanese and foreign patient populations. The incidences of some adverse events were higher in the Japanese than foreign patient population, although exposure was less in the former than the latter. Foreign data were extrapolatable to Japan. However, different recommended doses were selected in Japan according to the pharmacokinetic profiles of eletriptan and to the incidence of its adverse events rates.

Sumatriptan Nasal Spray (IMIGRAN® Nasal Spray, Figs. 4 and 5)

Two dose-response studies were conducted in Japan. In these studies, the primary endpoint for efficacy (headache relief rate within 2 hr after administration) did not show dose dependency. The applicant considered the reason which they did not clarify the efficacy criteria and why they used a scale of headache severity which was different from that used in the foreign studies. Consequently, they reanalyzed

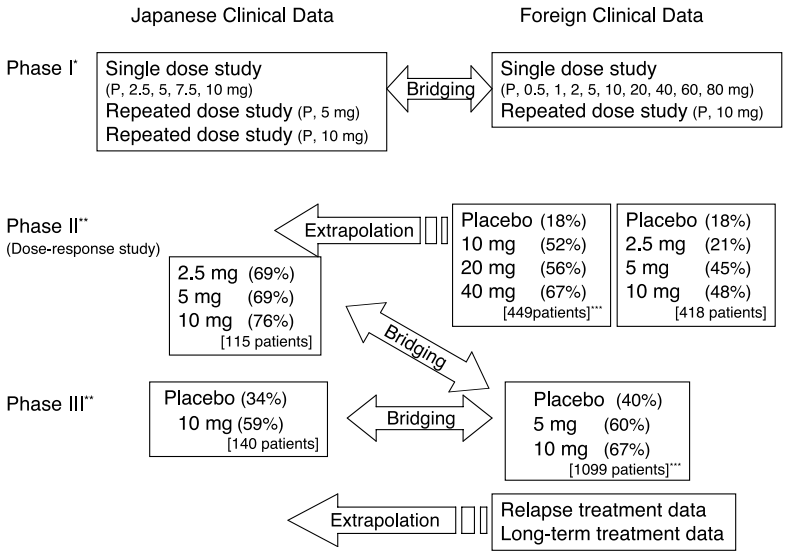

Fig. 6. Clinical Data Package of Rizatriptan Benzoate Tablets (Application)

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III; ( ): Headache relief rate within 2 hr after administration. [ ]: Number of patients who received the investigational drug. ***: The sumatriptan group was included.

one of Japanese dose-response studies using the same scale of headache severity as that used in the foreign studies. The results of the reanalysis demonstrated dose dependency for efficacy, leading the applicant to consider that the results were usable as "a bridging study." However, they followed advice on clinical trials from the regulatory authorities and conducted the Phase III clinical trial (placebo and 20 mg groups) as a bridging study. Subsequently, they considered that the foreign dose-response data were extrapolatable to Japan and might serve to define the recommended therapeutic dose in Japan (Fig. 4).

On the other hand, the regulatory authorities assessed that dose-response curves of sumatriptan were not extrapolatable to Japan because the Japanese Phase III study had only two groups (placebo and 20 mg groups). Only the relapse treatment data could be extrapolated (Fig. 5). The recommended therapeutic dose (20 mg) confirmed its efficacy and safety at the following points: the Japanese Phase III clinical trial revealed significantly higher efficacy in the 20 mg group than in the placebo group; exposure to nasal spray in a single dose was equivalent to that of tablet and injection in a single dose when efficacy was evaluated; and neither dose-dependent nor nasal spray-specific adverse events were observed.

Rizatriptan Benzoate Tablets (Maxalt® Tablets, Figs. 6 and 7)

The applicant intended to use the Japanese dose-response study (2.5, 5, and 10 mg groups) and the Japanese Phase III clinical trial (placebo and 10 mg groups) as bridging studies. They compared these studies with the foreign Phase III study (placebo, 5, and 10 mg groups; sumatriptan 100 mg group) and tried to extrapolate the dose-response relationship in the foreign study to Japan (Fig. 6).

The regulatory authorities did not agree to the applicant about this bridging because the design of the Japanese dose-response study was different from that of the counterpart study. On the other hand, the Japanese Phase III study was designed based on the counterpart study, leading to an assessment that the former was a bridging study. The adequacy of rizatriptan dose (10 mg) in the Japanese Phase III study could be supported by the Japanese dose-response study in which the 10 mg group was the most effective among the three groups. Finally, the results from the relapse treatment, repeated administration, and long-term treatment trials could be extrapolated to Japan (Fig. 7).

Drug Sensitivity to Ethnic Factors: Common Issues of Five Bridging Strategies

Ethnic factors need to be assessed in a bridging strategy before its planning. The extrinsic ethnic factors considered for triptans were disease definition, therapeutic approach, and patient profiles (*e.g.*, distribution of age, gender, and migraine type), etc. In the dose-response studies of sumatriptan Tablets, the complication rate of migraine and tension-type head-

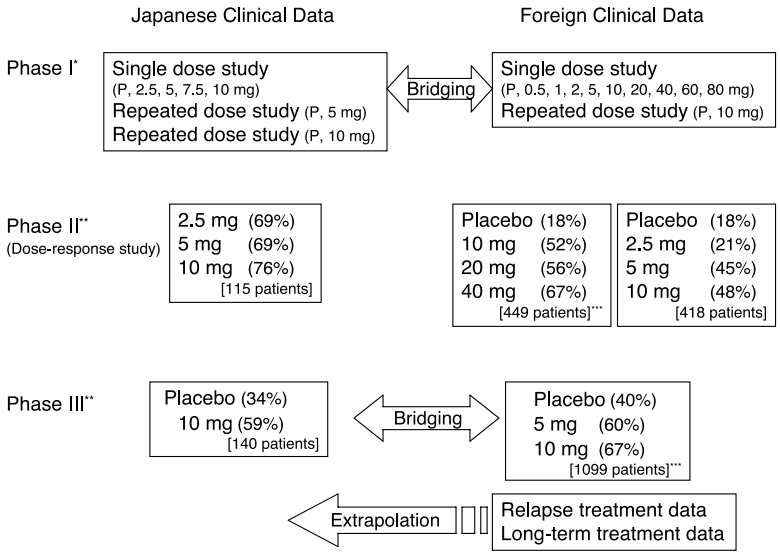

Fig. 7. Clinical Data Package of Rizatriptan Benzoate Tablets (Approval)

*: Phase I; ( ): Drug administration groups. P: Placebo. **: Phase II and III: ( ): Headache relief rate within 2 hr after administration. [ ]: Number of patients who received the investigational drug. ***: The sumatriptan group was included.

ache was higher in the Japanese patient population than in the foreign patient population. However, the applicant indicated that the complication rates between the Japanese and foreign patient populations were not significantly different epidemiologically. The extrinsic ethnic factors, including distribution of migraine types, were considered not to interfere with the extrapolation of foreign clinical data in each application.

Sensitivity to intrinsic ethnic factors was assessed in each application. Triptans are slightly sensitive to ethnic factors (*e.g.*, metabolism by enzymes known to show genetic polymorphism). However, the properties of triptans do not interfere with the extrapolation of foreign clinical data to Japan.

DISCUSSION

In Japan, a total of 26 NDAs were approved through a bridging strategy between 1999 and 2003. The NDAs of triptans accounted for five of 26 and constituted the largest target diseases field.[6] We can learn the design of a bridging strategy and consider that the extrinsic ethnic factors relating to migraine attack treatment did not interfere with the extrapolation of foreign data through the accumulation of these bridging experiences. In the development of a triptan in Japan, the foreign clinical data might be extrapolated without difficulty.

We classified the bridging strategies for triptans into two categories to be described below. One was to conduct a placebo-controlled dose-response study as a bridging study in an attempt to extrapolate the pivotal Phase III studies including a repeated dose study. According to this strategy, the applicant can provide rationale for dose determination in a new patient population without the need of conducting a Phase III clinical trial. To perform a bridging study by a comparable design, it is important to compare the results of two patient populations. This strategy was chosen and succeeded in the development of zolmitriptan, sumatriptan succinate, and eletriptan.

Another was related to sumatriptan Nasal Spray and rizatriptan benzoate Tablets. In their application, the placebo-controlled Phase III studies were regarded as bridging studies. A dose-response study in the Japanese patient population, in which no placebo-controlled group was established, was not planed as a bridging study and did not show dose dependency for efficacy. The applicants initially intended to extrapolate the foreign dose-response relationships because they were required to provide rationales for dose determination in Japan. Although Japanese regulatory authorities did not permit the use of dose-response curves in foreign studies because they could not evaluate dose-response equivalency between the two regions, they found supporting data for dose determination in the Japanese studies.

The above type of bridging strategies may be selected when the applicant changes its strategies.

When the applicants planned Phase III studies as bridging studies, they probably changed their strategies after the dose-response studies. We cannot describe accurately when the applicant chose a bridging strategy because detailed information regarding development time-line is not available to the public. However, we could know that some applicants changed the strategy in the course of clinical trials (*e.g.*, zolmitriptan Tablets) after the guideline was implemented.

When the applicant chose a bridging strategy, a successful placebo-controlled study in Japan was essential to get approval. Approximately 200 patients were enrolled in each placebo-controlled study, which was less than half of that in the foreign placebo-controlled study. In addition, the efficacy of relapse treatment was not verified in Japan. The applicant could reduce the number of trials and/or sample size, even if both a dose-response study and a Phase III study had to be conducted in a new region. Consequently, clinical development periods in the new region might have been shortened.[6)]

Some applications (*e.g.*, sumatriptan Nasal Spray) had predefined the statistical criteria for a bridging study to evaluate comparability between two patient populations. However, these criteria did not satisfy the regulatory authorities. Comparability between a bridging study and its counterpart study was evaluated on various perspectives, *e.g.*, headache relief rate, percentage of pain-free patients, and time-course of headache relief rate.

No comparators (*e.g.*, other triptans) were available when these five triptans were developing in Japan. Therefore, the status of triptans among existing drugs for migraine attack treatment was not discussed in these five applications. However, any new triptan to be developed in the future in Japan will be necessarily required to be compared with triptans (*e.g.*, sumatriptan) available in Japan.

In conclusion, acute migraine treatment is one of the therapeutic categories in which a bridging strategy is applicable to develop a new drug in Japan. The bridging strategy is useful to minimize the number of clinical trials and their participants in Japan.

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