Regulatory and operational challenges in conducting Asian International Academic Trial for expanding the indications of cancer drugs

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Abstract
There are many differences between Asian regions in terms of the regulatory requirements and operational procedures in conducting international academic clinical trials for the approval of new drugs. The National Cancer Center Hospital in Japan has launched an international investigator-initiated registration-directed trial (IIRDT) in Japan, Korea, Taiwan, and Singapore, aiming at obtaining pharmaceutical approval in participating regions. Differences in regulatory and operational procedures were identified while coordinating the trial. In Japan, regulatory authority reviews should be performed after approval by institutional review boards for IIRDT, whereas in other regions these can be done in parallel. There were disparities in Good Manufacturing Practice-related documents between regions. Several differences were found regarding investigational product (IP) management, specifically concerning labeling, import/export procedures, and customs clearance costs. On the other hand, safety reporting procedures were relatively well-harmonized in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A). Regions also differed in per-patient costs, due to varying regulations for academic registration-directed trials. In conclusion, the observed differences among Asian regions should be harmonized to facilitate international academic trials in Asia and thus resolve unmet patient needs worldwide.

Study Highlights
WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
International clinical trials have become common because they make it possible to accrue patients faster and obtain new drug approval in wider areas. However, pharmaceutical regulatory differences hinder the efficient conduct of international clinical trials, especially in academia.
INTRODUCTION

International clinical trials have become common because they make it possible to accrue patients faster and obtain new drug approval in wider areas, although there are some complexities in conducting trials, such as the need to identify intrinsic and extrinsic factors and different regulations of each country. The number of international industry-sponsored trials is increasing and the speed of treatment development has been accelerated. However, although pharmaceutical companies are eager to invest in common cancers, they are not always interested in rare cancers or multimodal treatments due to small market sizes, despite unmet medical needs. In order to meet such needs, international academic clinical trials should play a larger role.

Many international clinical trials are conducted by academic research groups in the United States and Europe. The population in Asian regions is growing and the average life expectancy is increasing, which will lead to more demand for international academic trials.

The National Cancer Center Hospital (NCCH) in Japan is one of the largest cancer research institutions in Asia. The NCCH has participated in numerous international industry-sponsored trials and has led a number of domestic academic clinical trials. Based on the expertise derived from this involvement, the NCCH has launched an Asian international investigator-initiated registration-directed trial (A-IIRDT) involving four Asian regions (Japan, Korea, Taiwan, and Singapore). As far as we know, this is the first study in Asia to be sponsored by an academic institution, with aims to obtain pharmaceutical approval in the participating regions.

To facilitate this A-IIRDT and further expand academic clinical trial networks in Asia, we describe the differences identified by the A-IIRDT regarding regulatory requirements and operational procedures in the four participating Asian regions.

METHODS

In 2018, the NCCH initiated an international randomized phase III trial in 4 regions in Asia: Japan, Korea, Taiwan, and Singapore (PATHWAY trial). Through the experience of coordinating that trial, we accumulated regulatory and operational information to inform the initiation and conduct of future academic trials in these regions. In this paper, we report differences in (a) the clinical trial review processes of regulatory authorities (RAs) and institutional review boards (IRBs), (b) investigational new drug (IND) dossiers, (c) IP management procedures, (d) safety reporting requirements, (e) study site procedures, and (f) subject reimbursement costs.

PATHWAY trial

The PATHWAY trial is a randomized, double-blinded, placebo-controlled, phase III trial for hormone receptor (HR)–positive, HER2-negative advanced, or metastatic breast cancer (NCT03423199). Palbociclib or placebo was administered in combination with tamoxifen. The primary end point is progression-free survival. A total of 185 patients has been randomized 1:1 to the palbociclib or placebo arm from 12 sites in Japan, 6 sites in Korea, 3 sites in Taiwan, and 2 sites in Singapore. Palbociclib was first approved in the United States in 2015, and, as of 2020, it has been approved in more than 90 countries. Palbociclib has been approved by the regulatory authorities in participating
regions in combination with letrozole for the treatment of postmenopausal women with locally advanced or metastatic HR-positive, HER2-negative breast cancer, and in combination with fulvestrant for the treatment of patients whose disease has progressed after endocrine therapy. However, the process of obtaining approval for cancer drug indications is generally fragmented; for example, the initial indications are for recurrent and metastatic disease, then for first-line therapy, and finally for postoperative adjuvant therapy; clinical trials are then needed to obtain additional indications. Thus, the PATHWAY trial was initiated to expand the indications of palbociclib in combination with tamoxifen in the participating regions. Therefore, the trial is being conducted in full compatibility with the International Conference on Harmonization–Good Clinical Practice (ICH-GCP). To achieve compliance with local regulations, the trial is being performed in Japan as an IIRDT in accordance with the Japanese Pharmaceuticals and Medical Devices Law. Details of Japanese regulation of academic clinical trials are described elsewhere. In other regions, the trial was conducted as a registration-directed trial, and clinical trial notifications (CTNs) were submitted to each local regulatory authority before trial initiation. The IPs, investigator’s brochure (IB), and safety information, such as the suspected, unexpected, serious adverse reactions (SUSAR) line listing, and the Development Safety Update Report (DSUR) were provided by Pfizer, the industry partner of the PATHWAY trial.

RESULTS

Clinical trial review processes of RAs and IRBs

Clinical trial review processes of RAs and IRBs are stipulated in GCPs, Pharmaceutical Affairs Laws, and other related regulations of each region. Clinical trial review processes of RAs and IRBs are shown in Table 1. There are no significant differences in regulatory review processes regardless of the presence of global regulatory approval. The most significant difference between countries is that in Korea, Taiwan, and Singapore, RA reviews of CTNs and IRB reviews are performed in parallel regardless of the type of study sponsor; in Japan, however, these are performed in parallel in industry-sponsored trials, whereas in IIRDTs, CTNs must be submitted after approval by at least one IRB.

IND dossiers

Table 2 shows the list of documents that should be attached to CTNs of approved drugs in each region. The regions differ in terms of the essential dossiers that require translation in the local language. In addition, there are disparities regarding Good Manufacturing Practice (GMP)-related documents. In principle, all nonclinical data related to the manufacture and quality of investigational drugs should be described in GMP documents. However, these can be omitted in Japanese registration-directed trials, and a cross-reference letter is valid in Korea to avoid duplicate submission by a marketing authorization holder (an owner of the Chemistry, Manufacturing and Control [CMC] information). When conducting a clinical trial using an investigational drug developed by academia, the GMP documents can be a hurdle for academic investigators. This process can vary depending on local regulations, the indication of the investigational drug, etc.

In the case of a registration-directed trial for a New Drug Application (NDA), compensation is required in all regions, in accordance with the ICH-GCP. In fact, the study sponsor purchased the clinical trial insurance in the PATHWAY trial, and an insurance certificate is required in Korea, Taiwan, and Singapore.

IP management procedures

Requirements for IP management are stipulated in GCPs, GMPs, and other related regulations. IP management procedures are summarized in Table 3. There were several differences between regions regarding labeling, import/export procedures, and the customs clearance cost. The shipping and storage procedures of IPs, including the approaches to label attachment and central storage, should be determined after thorough exploration of local regulations concerning customs clearance and import/export expenses.

Safety reporting

Requirements for safety reporting to regulatory authorities are stipulated in Safety Reporting Regulations of each country. Each site investigator should report to the IRB all serious adverse events that occur at their site according to the site standard operating procedures (SOPs) listed in Table 4, which demonstrate slight differences in reporting deadlines between regions and institutions. Each site investigator should also immediately report all serious adverse events to the study sponsor. The reporting procedure and deadline are specified in the protocol so that there is no difference between regions. Although the study sponsor should report all SUSARs to regulatory authorities according to ICH of Technical Requirements for Pharmaceuticals for Human Use, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH-E2A), there are
| Regulatory authority | Japan | South Korea | Taiwan | Singapore |
|----------------------|-------|-------------|--------|-----------|
| PMDA                 | MFDS  | TFDA        | HSA, the MOH |
| MHLW                 | NIFDS | DOH         |        |
| MFDS                 |       | CDE         |        |

| Related regulations | Japan-GCP<sup>5</sup> | Korean-GCP<sup>6</sup> | Taiwan-GCP<sup>7</sup> | ICH-GCP<sup>8</sup> |
|---------------------|-----------------------|------------------------|------------------------|---------------------|

**IND and IRB review process**

- **Industry-sponsored trials:** parallel review possible.
- **IIRDT:** submit IND after IRB approval.
- **Parallel review is possible.**
- **Parallel review is possible.**
- **There are 3 clinical trial submission routes:**
  1. **CTA,** for trials on locally unregistered therapeutic drugs or locally registered but not used in accordance with approved indications
  2. **CTN,** for trials on locally registered therapeutic drugs used in accordance to its approved indications
  3. **CTC,** for trials of medicinal products (cell, tissue, and gene therapy products or complementary health products)

**Local IND holder / in-country clinical caretaker**

- **Required** (investigator can be IND holder in IIRDT)
- **Required**
- **Required** (a power of attorney is submitted to DOH by study sponsor)
- **Required**

**IND application form and language**

- **Clinical trial notification form (in Japanese)**
- **IND application can be made through web site (in Korean)**
- **The official application format is in Chinese. English is acceptable.**
- **IND application can be made through web site (in English)**

**Requirements regarding IND amendments**

- **Major revisions require timely IND amendment.**
- **IND amendment is required for any revision of protocol or IB.**
- **IND amendment is required for any revision of protocol, ICF, or IB.**
- **IND amendment is required for any revision of protocol or IB.**
- **Progress/Annual Report is required every 6 months.**

**Requirements of local patient data for a New Drug Application**

- **Japanese data required.**
- **Participation of domestic medical institutions required.**
- **Taiwanese data required.**
- **The required number of subjects varies depending on the trial scale and the presence of FDA/EMA approval.**
- **Singaporean data are not mandatory for drugs already approved in overseas countries.**

**Clinical Trial Compensation Guidelines**

- **Japanese-GCP<sup>5</sup>**
- **Korean-GCP<sup>6</sup>**
- **Taiwan-GCP<sup>7</sup>**
- **ICH-GCP<sup>8</sup>**
  - The Association of the British Pharmaceutical Industry Guideline<sup>30</sup> (Reference)
some differences in requirements depending on drug approval status.

**Study site procedures**

All sites participating in the PATHWAY trial have previous experience participating in one or more global industry-sponsored trials, as well as well-standardized systems, such as IRBs, clinical research coordinator (CRC) support, and investigational drug management, with minor differences, as summarized in Table 5.

**Subject reimbursement costs**

There were differences between regions in the reimbursement of clinical trial costs by public health insurance. In Japan, for example, 70–90% (depending on age) of fees for examinations, such as blood and imaging tests and for concomitant medications, are covered by public health insurance, and the remaining 10–30% is paid by the patients, according to “Special or Specified Medical Care Coverage.” When a clinical trial is conducted as an industry-sponsored trial, the sponsor should pay all of these costs. In Korea, Taiwan, and Singapore, on the other hand, these costs must be fully covered by sponsors of registration-directed trials, regardless of whether they are industry-sponsored or academia-initiated. Table 6 shows estimations of the average annual examination fee per subject based on the PATHWAY trial, assuming a standard phase III oncology trial.

**DISCUSSION**

This study is the first to elucidate regulatory and operational differences between countries identified while conducting an academic international IIRDT. The four regions demonstrated discrepancies in RA and IRB clinical trial review processes, IND dossiers, and IP management procedures; on the other hand, safety reporting procedures were relatively well-harmonized in accordance with ICH-E2A guidelines. In most Asian countries in particular, such regulatory and operational information is not translated into English (with the exception of Singapore, where English is the official working language); therefore, the results described here will be of great help in conducting academic clinical trials in Asia.

If the original English version is accepted for all CTN dosiers submitted to each regulatory authority, the burden on academia will be reduced. On the other hand, it may be reasonable to use local languages for some study documents submitted to study sites and IRBs, because these documents are utilized by many local users.

Operational issues can be managed by understanding local procedures in each country, but financial issues can be the most difficult barrier in international trials. For example, per-patient costs vary between regions due to differences in regulations of academic registration-directed trials. Japan has an IIRDT regulation that enables investigators to be study sponsors, and a proportion of the per-patient cost is reimbursed by public health insurance. For example, the costs of examinations and concomitant medications are covered by public health insurance based on “Special or Specified Medical Care Coverage.” On the other hand, in Korea, Taiwan, and Singapore, the study
|                | Japan                                      | South Korea                                            | Taiwan                                      | Singapore                                   |
|----------------|-------------------------------------------|--------------------------------------------------------|---------------------------------------------|---------------------------------------------|
| **Protocol**   | Yes (in Japanese)                          | Yes (in Korean)                                        | Yes                                         | Yes (in English)                            |
|                | Korean protocol synopsis is also required. |                                                        |                                              |                                              |
| **ICF**        | Yes (in Japanese)                          | Yes (in Korean)                                        | Yes (in Chinese)                            | Yes (in English)                            |
| **IB**         | Yes (in Japanese)                          | Yes (in Korean)                                        | Yes                                         | Yes (in English)                            |
|                | Local formatting changes are not needed.   | Korean summary of IB is also required.                  |                                              | Local formatting changes are not needed.    |
|                | Annual IB update is required.              | Local formatting changes are not needed.               | Annual IB update is required.               | Annual IB update is required.               |
| **Investigator’s CV** | No                                         | No Information of investigational sites, investigators is required. | Yes                                         | Yes                                         |
|                | Information of investigational sites, investigators is required. | Yes For both PI and Sub-I, either Chinese or English version is acceptable. |                                             | CV of PI in English is required.            |
| **CRF**        | No                                        | No CRF template is not necessary.                      | Yes                                         | Yes (in English)                            |
|                | CRF template is not necessary.             |                                                        |                                              |                                             |
| **Study subject compensation documents** | No                                         | Yes (subject compensation letter and insurance certificate) | Yes (insurance certificate)                  | Yes (insurance certificate)                  |
| **CMC documents** | No                                        | Yes If the original document is written in foreign language, Korean document should be attached to the original document. | Yes CMC data is required either in English or Chinese. | Yes                                         |
| **GMP certificate of the investigational drug** | No                                        | Yes If the original document is written in foreign language, Korean document should be attached to the original document. | Yes                                         | Yes                                         |
|                | GMP certificate of the investigational drug |                                                        |                                              |                                              |
| **DSUR**       | Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted. | Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted. | Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted. | Yes If another sponsor such as a Marketing Authorization Holder has created a DSUR for the study drug and submitted it to the regulatory authority, it can be omitted. |

Abbreviations: CMC, chemistry, manufacturing, and control; CRF, Case Report Form; CTN, clinical trial notification; CV, curriculum vitae; DSUR, Development Safety Update Report; GMP, good manufacturing practice; IB, investigator brochure; ICF, informed consent form; IND, investigational new drug; IP, investigational product; PI, principal investigator; Sub-I, sub-investigator.
### TABLE 3  Investigational product management procedures

| Procedure for IP import / export | Japan | South Korea | Taiwan | Singapore |
|----------------------------------|-------|-------------|--------|-----------|
| Drug import license or Yakkan certificate is not required. Only CTN is needed to pass customs clearance. | Drug import license is not required. Standard Customs Clearance Schedules Report form needs to be issued by Korea Pharmaceutical Trading Association. Annual update required. | IP import license is required. The license specifies the valid period and upper quantity limit. It takes 3–4 weeks to obtain or update the license. | IP import license is not required. Clinical Research Material Notification needs to be submitted to the Health Science Authority by the study sponsor at time of study license application or after obtaining the study license. |

| Items to be listed on the IP label | Japan | South Korea | Taiwan | Singapore |
|-----------------------------------|-------|-------------|--------|-----------|
| For clinical trial use (protocol number) | For clinical trial use (protocol number) | For clinical trial use (protocol number) | For clinical trial use (protocol number) |
| Title and address of the sponsor-investigator | Study sponsor (Local IND holder) | Study sponsor | Study sponsor |
| Chemical Name/Laboratory code | Chemical Name/Laboratory code | Chemical Name/ Laboratory code | Chemical or name of substance, strength or potency, quantity of units |
| Lot or batch number identifying content and packaging operation of the product | Quantity per IP bottle | Quantity per IP bottle | Lot or batch number identifying content and packaging operation of the product |
| Storage Conditions | Storage Conditions | Storage Conditions | Expiration date |
| Dosage and administration | Lot or batch number identifying content and packaging operation of the product | Lot or batch number identifying content and packaging operation of the product | |
| Expiration date | Expiration date | Expiration date | |
| Quantity per IP bottle (if necessary) | Dosage and administration | Expiration date | Manufacturing date |
| Storage Conditions | Lot or batch number identifying content and packaging operation of the product | Expiration date | |
| Chemical or name of substance, strength or potency, quantity of units | Name/Laboratory code | Name/Laboratory code | |
| Storage Conditions | Pharmaceutical form, Dosage and route of administration | Pharmaceutical form, Dosage and route of administration | |
| Lot or batch number identifying content and packaging operation of the product | | Lot or batch number identifying content and packaging operation of the product | |
| Manufacturing date | Expiration date | Expiration date | |

Abbreviations: CTN, clinical trial notification; IND, investigational new drug; IP, investigational product.
# Table 4  Safety reporting requirements

| Japan | South Korea | Taiwan | Singapore |
|-------|-------------|--------|-----------|
| **Safety Reporting Regulations** | • Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (PAB/ED No. 227 dated March 20, 1995) \(^{20}\)  
• Reporting of Adverse Drug Reactions Occurring in Clinical Trials to PMDA (PFSB Notification No. 0330001 dated March 30, 2004) \(^{21}\) | • Korean-GCP  
• Korea MFDS guidelines on SUSAR reporting\(^ {22}\) | • Taiwan-GCP  
• Taiwan National Adverse Drug Reactions Reporting system Q&A\(^ {23}\) | • ICH-GCP  
• Expedited Safety Reporting Requirements for Therapeutic Products and Medicinal Products used in Clinical Trials\(^ {24}\) |

| Safety Reporting to regulatory authority (in case drug is approved) | • Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator’s awareness  
• Non-death or non-life threatening cases (only SUSARs), death or life-threatening cases (non-SUSARs); within 15 calendar days from the investigator’s awareness  
• Research Reports  
• Reports of Safety Measures  
• Annual safety update (DSUR) | • Death, fatal, or life-threatening cases (only SUSARs); within 7 calendar days from the investigator’s awareness  
• Non-death or non-life-threatening cases (only SUSARs); within 15 calendar days from the investigator’s awareness  
• Annual safety update (DSUR) | • Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator’s awareness  
• Non-death or non-life-threatening cases (only SUSARs); within 15 calendar days from the investigator’s awareness  
• Annual safety update (DSUR) | • Death or life-threatening cases (only SUSARs); within 7 calendar days from the investigator’s awareness  
• Non-death or non-life-threatening cases (only SUSARs); within 15 calendar days from the investigator’s awareness  
• Annual safety update (DSUR) |

Abbreviations: DSUR, development safety update report; GCP, good clinical practice; ICH, International Council for Harmonisation; MFDS, Ministry of Food and Drug Safety; PAB/ED, Pharmaceutical Affairs Bureau / Examination Division; PESB, Pharmaceutical and Food Safety Bureau; PMDA, Pharmaceuticals and Medical Devices Agency; Q&A, questions and answers; SUSAR, suspected, unexpected, serious adverse reaction.
| Study site procedures | Japan | South Korea | Taiwan | Singapore |
|-----------------------|-------|-------------|--------|-----------|
| Certification of study site by the government | No | Yes: Certified by MFDS according to Ordinances for Institution Designation | Yes: Available only at government-certified medical sites | No |
| IRB | Central IRB is applicable (not mandatory) | Central IRB is applicable (not mandatory) | Central IRB is applicable (central IRB is recommended but not mandatory for multicenter trials) | Central IRB is applicable |
| Renewal of IRB approval | Required (annually) | Required (annually) | Required (annually) | Required (annually) |
| ICF language | Japanese | Korean | Chinese | English, Chinese, Tamil, and Malay |
| IRB information and investigator name should be described in accordance with Japanese GCP requirements | If gene-/embryo cell-related testing is included, additional ICF is required (Bioethics and Safety Act, Article 24. Consenting to Genetic test)³¹ | If central IRB is used, informed consent form template of TFDA shall be used (CDE Notification 2017/9/26)³² | |
| Language of clinical trial agreement (for international clinical trials) | Japanese in principle (English with translation can be used in some sites) | English available | Chinese in principle (English with translation can be used in some sites) | English |
| SAE reporting timeline to IRB | Immediately submit all relevant institutional SAE reports to the head of the medical institution/IRB (per site’s own SOP) | Death or life-threatening cases (including SUSARs); within 7 days from the investigator’s awareness and within 15 days from the initial reporting SAE; within 15 days from the investigator’s awareness. Accumulated SAE data will be submitted every 6 months (per site’s own SOP) | Death or life-threatening cases (including SUSARs); within 7 business days from the investigator’s awareness Non-death or non-life-threatening cases (including SUSARs); within 15 business days from the investigator’s awareness (per site’s own SOP) | Death or life-threatening cases (only SUSARs); within 24 h from the investigator’s awareness Non-death or non-life threatening case (only SUSARs); not later than 15 calendar days from the investigator’s awareness (per site’s own SOP) |
| Accessibility to source data documents during monitoring/audit² | No restriction | No restriction | No restriction | Certified copy checks (the policy was not to grant CRAs or Auditors access to electronic health records) Occasional spot-checks of electronic health records by CRAs allowed with site supervision and over-the-shoulder access. |

Abbreviations: CDE, Center for Drug Evaluation; CRA, clinical research associate; GCP, good clinical practice; ICF, informed consent form; IRB, institutional review board; MFDS, Ministry of Food and Drug Safety; SAE, serious adverse event; SOP, standard operating procedures; SUSAR, Suspected, Unexpected, Serious Adverse Reaction; TFDA, Taiwan Food and Drug Administration.

²Status at participating sites in the PATHWAY trial.
TABLE 6 Subject examination fee borne by study sponsor (based on the PATHWAY investigator-initiated trial experience)

| Region     | Fee (Study treatment duration, 13 months) |
|------------|-----------------------------------------|
| Japan      | US $50\* Special or specified medical care coverage |
| South Korea| US $5,500–15,000                        |
| Taiwan     | US $10,000–12,000                       |
| Singapore  | US $10,000–14,000                       |

\*Partial expenses such as infectious disease test, pregnancy test, image copying fee, etc. are borne by each hospital.

CONCLUSIONS
During an academic registration-directed trial in Asia, several differences regarding regulatory and operational procedures were noted between regions. These differences should be harmonized to facilitate international academic trials in Asia and thereby resolve unmet patient needs.

CONFLICT OF INTEREST
The PATHWAY trial was funded by and conducted as a clinical research collaboration with Pfizer. Outside of the submitted work, the following authors report grants and/or other payments: K.N. reports personal fees from Taiho Pharmaceutical, Chugai Pharmaceutical, and Bayer. K.Y. reports personal fees from Novartis, Ono Pharmaceutical, Chugai Pharmaceutical, Eisai, Pfizer, AstraZeneca, and Taiho Pharmaceutical. E.N. reports personal fees from Pfizer, Nippon Kayaku, Sysmex, Eli Lilly, and AstraZeneca. Y.S.L. reports personal fees from Pfizer, Novartis, Eli Lilly, Eisai, Roche, and Merck Sharp & Dohme; grants from Novartis, Merck Sharp & Dohme, and Roche. Y.S.Y. reports personal fees and/or nonfinancial support from AstraZeneca, Pfizer, Novartis, Lilly, MSD, Eisai, and Roche. K.T. reports grants from Pfizer, Daiichi-Sankyo, Eli Lilly, Chugai, AstraZeneca, Merck Sharp & Dohme, and Novartis. Y.F. reports other payments from Japan Agency for Medical Research and Development, and the Ministry of Health Labour and Welfare of Japan, during the conduct of the study, and contributed to the PATHWAY trial until March 2019; Y.F. also received honoraria from Astra Zeneca, Daiichi Sankyo, Taiho Pharmaceutical, Chugai Pharmaceutical, Novartis Pharma, SRL, Bristol-Myers Squibb, and Santen Pharmaceutical outside the submitted work. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
T.H., K.N., E.N., and Y.F. wrote the manuscript. T.H., K.N., K.Y., E.N., M.W., K.T., and Y.F. designed the research. T.H., K.N., E.N., and Y.F. analyzed the data.

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