Listen to a recording of this issue

The Altascientist
SCIENTIFIC JOURNAL
ISSUE NO. 24

SHORTENING DRUG DEVELOPMENT TIMELINES WITH ASIAN ETHNOBRIDGING TRIALS

Developing drugs for the Asian market may require that Phase I studies be repeated in regions outside North America or Europe, to determine whether the pharmacokinetics of the investigational drug are equivalent in different ethnic groups. Asian ethnobridging is a strategy to demonstrate biosimilarity of drug products between Asian and non-Asian populations by comparing pharmacokinetics of the investigational drug in both ethnic groups, considering both intrinsic and extrinsic factors.

Conducting ethnobridging studies locally, during Phase I, in the target population, can reduce drug development timelines by the number of years typically needed to complete clinical development in the target region, as compared with North America or Europe. A Phase I ethnobridging strategy allows you to recruit patients in "global" safety and efficacy trials (Phases II and III) without repeating Phase I development in that region and population.

WHY ASIAN ETHNOBRIDGING?

Over 60% of the world's population is considered part of the diverse group of ethnicities commonly referred to as Asian, with each ethnicity having a distinct genetic profile. A 2019 systemic review[1] identified 49 different ethnic categories that were classified as "Asian" in pharmacogenetic studies. Within Asian subgroups, the known differences in pharmacogenetics are generally previously identified variants, which are significantly more or less prevalent in Asians as compared to other populations.

Two identified intrinsic factors that affect drug metabolism are that Asians are more commonly poor metabolizers of cytochrome P450 (CYP) 2C19, and carriers of the human leukocyte antigen (HLA)-B*15:02 allele. The relative risk increase was shown to vary between genes and drugs but could be more than 100-fold higher in Asians. The resulting adverse events that are more prevalent in Asians range from reduced drug efficacy to severe cutaneous skin reactions.[1]

Extrinsic factors (e.g., diet and lifestyle), socioeconomic factors, environmental influences (e.g., amount of sunshine, and air and water quality), as well as differences in medical practice, may have an impact on the pharmacokinetics (PK) of certain drugs in Asian populations.

Because of these differences, drugs were generally developed in Asia on a timeline that was different from the Western regions of the world. By the late 90s and early 2000s, a drug development time-lag of as much as eight to 10 years was observed by consumers for drugs (many for the most critical indications such as cancer and heart disease) to reach Asian markets. The Japanese health authorities were first to respond to this outcry and instituted some short-term solutions:

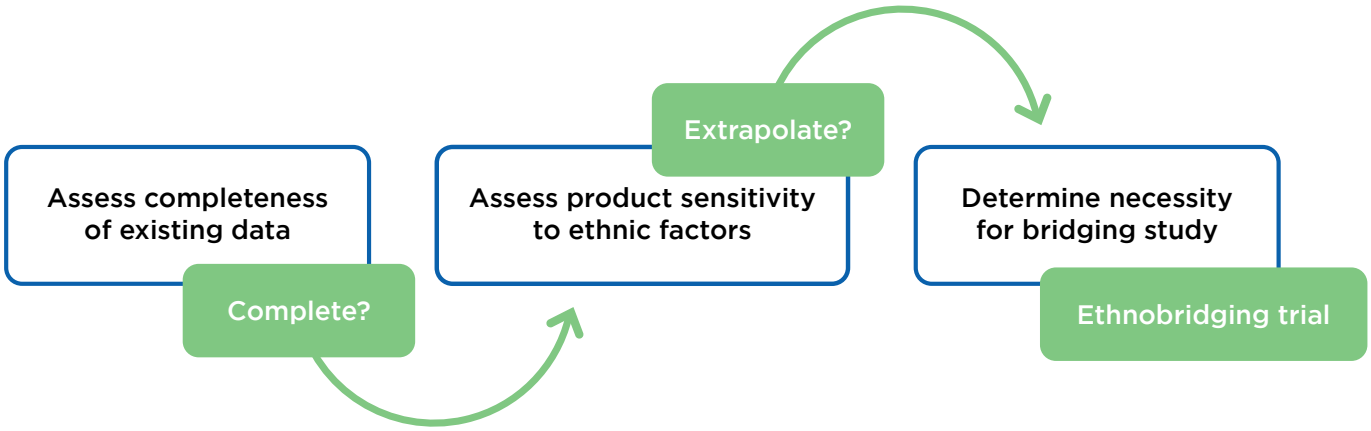
- Modified drug pricing system
  - Certain drugs still under patent were exempted from biennial price reduction
- The Ministry of Health, Labour and Welfare (MHLW) identified:
  - 109 prescription medications to receive prompt reimbursement decisions
  - 91 new chemical entities (NCEs) requiring expedited development by pharmaceutical companies
  - 200 Japanese institutions to prescribe unlisted drugs to meet identified unmet medical needs

Also, to address this lag, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) issued the ICH E5 guidance, which provides a strategy to bridge data from a completed dossier in one region to another region to speed up approval and minimize duplication of clinical trials. The Japanese health authorities, along with Korea and Taiwan, rapidly voiced their firm support of ICH E5.

THE ICH E5 GUIDANCE

The ICH E5 was accepted in Japan in 2007. The guidance provides bridging requirements, and suggests that global or multi-regional development is a more efficient strategy to improve the drug lag. Sponsors must have a complete clinical data package, including adequate characterization of PK/PD, efficacy and safety, and clear definition of dose response. Authorities will also review acceptability of evaluation of clinical disorders in that region, ensuring that medical and diagnostic approaches used are relevant to the new region. Once all the relevant data is provided and reviewed, a bridging strategy could be considered for implementation. Three steps would tell if a drug could be bridged or not, see Figure 1.

Figure 1. Three Steps for Determining Ethnobridging Requirements



THE ICH E17 GUIDANCE

The ICH E5 guidance is the accepted solution to the drug development lag between the West and other global regions. In November 2017, the ICH published E17, which is further guidance and context for multi-regional clinical trials (MRCTs) in support of global drug development. It includes direction on the use of good clinical practice, statistical principles for sample sizes and control groups, and genomic sampling. The ICH website also offers a business plan, relevant presentations, and a training module.

The guidance addresses strategic program considerations and issues that are specific to the planning and design of confirmatory MRCTs, and should be used together with other ICH guidances for industry, including:

- E5 Ethnic Factors in the Acceptability of Foreign Clinical Data
- E6 Good Clinical Practice
- E8 General Considerations for Clinical Trials
- E9 Statistical Principles for Clinical Trials
- E10 Choice of Control Group and Related Issues in Clinical Trials
- E18 Genomic Sampling and Management of Genomic Data

> “...may enhance scientific knowledge about how treatment effects vary across regions and populations under the umbrella of a single-study protocol, and how this variation may be explained by intrinsic and extrinsic factors of drug exposure.”
>
> **- ICH E17**

MRCTs conducted according to the specifications contained within E17 and related guidances will allow investigation of treatment effects, including safety evaluations in the overall population and investigation of the potential impact of intrinsic and extrinsic factors, or ethnic factors, on the treatment effect.

According to the ICH, the guidance may also facilitate more efficient drug development by increasing the possibility of submitting marketing authorization applications to multiple regulatory authorities in different regions simultaneously, and thereby provide earlier access to new drugs worldwide.

If a bridging strategy is determined to be relevant for a particular drug development program, additional considerations about the regions of development and specific approaches are important to understand.

ACCELERATING ASIAN DRUG DEVELOPMENT

When a drug is being developed mainly for the U.S. and Japanese market, with a bridging strategy, a typical development program would consist of an IND and NDA in the U.S., followed by Japanese bridging studies, and completed with Phase II onwards in both the U.S. and Japan. This approach eliminates the necessity to duplicate the first-in-human and SAD/MAD portions in both regions, thereby reducing costs and shortening the NDA timeline (Figure 2).

Additionally, the SAD/MAD design of trials conducted in the original region can be enhanced by including subjects from the proposed ethnic population in each of the cohorts. By having these subjects included in the healthy normal cohorts up front, we can analyze simultaneously and obtain earlier signal for whether bioequivalence and bioavailability are similar in the Asian population compared to the Western subjects. The results of that analysis will then inform decisions for next steps in the global drug development plan. An example of such an enhanced design is shown in Figure 3.

Figure 2. Japanese Bridging Strategy

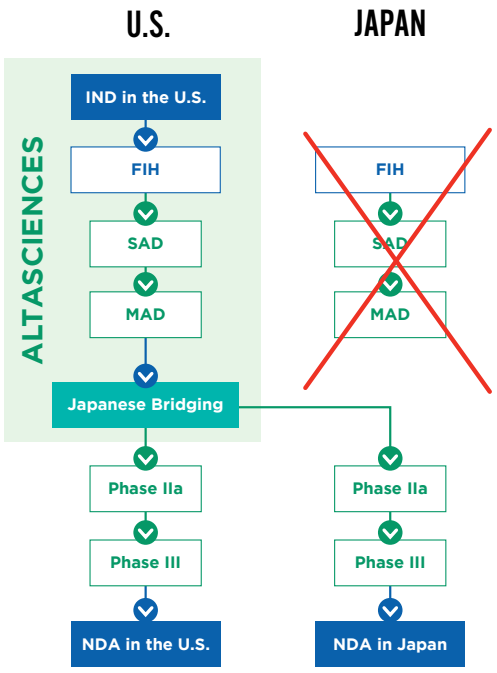
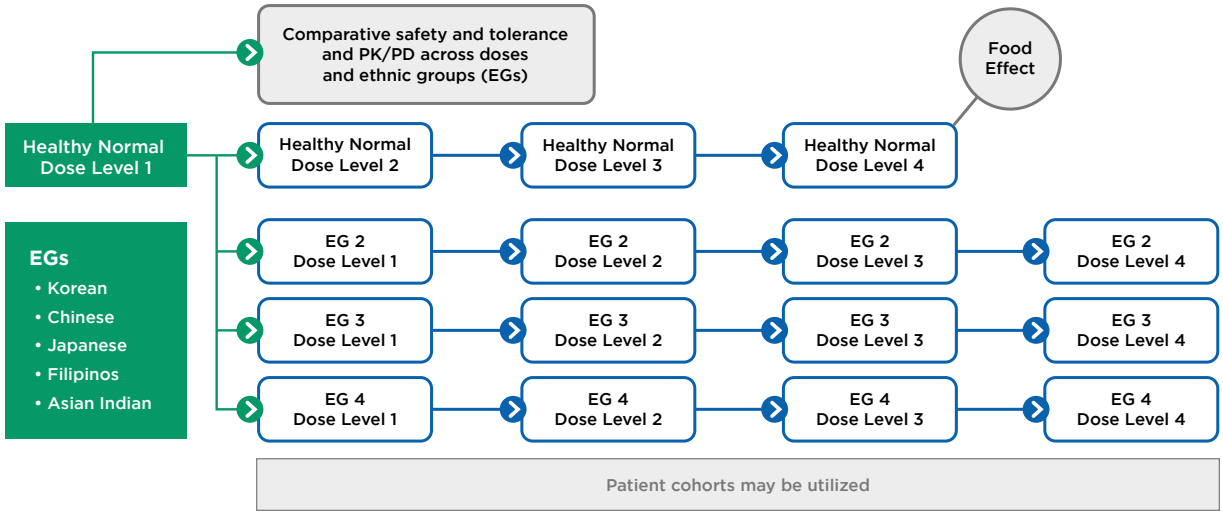


Figure 3. Enhanced Design Concept Multiple Asian Regions



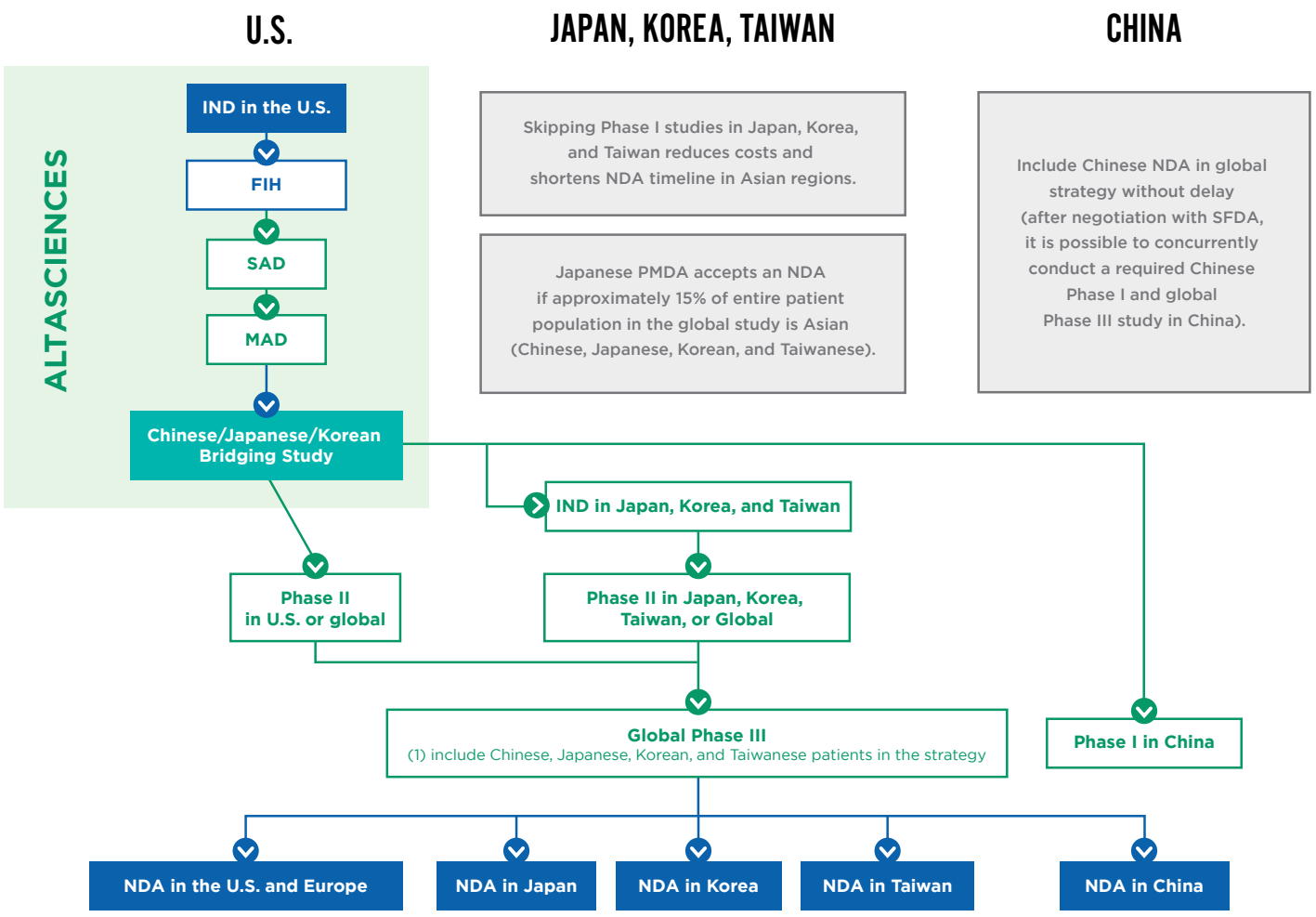
Consultation with the Pharmaceutical and Medical Devices Agency (PMDA) in Japan is possible prior to starting global clinical trials (GCTs), and is an opportunity to clarify requirements and ensure regulatory authority buy-in prior to starting development work. The optional consultation is provided on a "for fee" basis at a cost of $30,000 to $60,000 USD at time of writing.

For sponsors who have the intention of developing a drug in all Asian markets simultaneously, the development plan would look similar to Figure 4. Initial (FIH, SAD/MAD, and bridging) trials would be conducted in the U.S., and target development regions and bridging strategies identified. After consultations with the regulatory authorities across the various regions, further decisions on how to complete the development plan would be made (one large global trial or regional development).

Note:

- PMDA in Japan will accept an NDA as long as approximately 15% of the entire patient population in a global study is Asian (Chinese, Japanese, Korean, and Taiwanese).
- Based on discussion with the Chinese State Food and Drug Administration (SFDA), it is possible to conduct a required Chinese Phase I and Global Phase III study in China concurrently.

Figure 4. Simultaneous Global Drug Development



LANGUAGE REQUIREMENTS FOR GCTS

An additional consideration for the conduct of regional or global trials is the requirement for study documentation to be provided in the local language of each region. Not all documentation is required in every region, and even where required, it need not always be translated. In certain cases, documents are not mandatory, or can be provided in English. The time and cost of providing such documentation in the different languages should be considered in the development plan and timeline.

DOCUMENT	JAPAN	KOREA	CHINA
Application Form	Yes (in Japanese)	Yes (in Korean)	Yes (in Chinese)
Protocol	Yes (in Japanese)	Yes (in Korean)	Yes (in English and Chinese translation)
Investigator's Brochure	Yes (in Japanese)	English is acceptable in the case of Phase I on healthy normal subject.	Yes (in English and Chinese translation)
CRF (sample)	CRF (sample) Not mandatory English is acceptable.	Yes (English is acceptable)	No
Informed Consent	Yes (in Japanese)	No need to submit	No
Investigator's CV	No	No	No

Experienced, Expert Support – Case Studies

Altasciences has extensive experience supporting Asian ethnobridging strategies, and our experts work closely with sponsors to develop an effective strategy for each drug development plan. A recent publication pointed out that over 90% of drugs planned for multi-regional clinical development underwent an Asian Bridging PK study in preparation for program launch.[2] Careful analysis and a thorough understanding of all the relevant factors, and a broad and deep knowledge of the regulations and requirements in each region ensure that the most efficient plan is put forward for each unique situation. Below are two case studies of ethnobridging trial support.

Case Study – Multiple Studies to Support Global Pharmaceutical Sponsor

Our extensive expertise allowed us to complete 22 Japanese bridging trials, involving 16 NCEs from 2016 to 2021 for a large, global pharmaceutical sponsor. To date, nine compounds have received PMDA approval. Two are currently in Phase II development in Japan, and five are awaiting sponsor or regulatory action.

16 Compounds tested → **11** Accepted by PMDA

5 Awaiting sponsor or regulatory action

Case Study – Ophthalmic Drug Development

In 2020, a sponsor developing an ocular medication approached Altasciences to conduct an ethnobridging study in 30 Japanese individuals, in support of GCTs. After 13 days of active recruitment, a cohort of 30 subjects was completed in a single day.

- Ethnobridging study with ocular assessments
- Completed recruitment of 30 Japanese healthy normal subjects in a single cohort
- Achieved a 100% completion rate by efficiently locating subsets of Asian patients, ensuring compliance, and narrowing eligibility prior to full screening

Study design features:

- Screening: Day -21 to Day -2
- In-Clinic Stay: Day -1 to Day 6
- Out-Patient Visit Days (4)
  - Day 7, Day 8, Day 16, and Day 35

START SCREEN	4/2/2020	First subject first dose (FSFD)	4/21/2020
END SCREEN	4/19/2020	Last subject first dose (LSFD)	4/21/2020
TOTAL SCREENING DURATION	17 total days (13 working days)	Subjects randomized	2 cohorts of 15 planned; completed in 1 cohort of 30
SUBJECTS SCREENED	71	Enrollment duration (FSFD to LSFD)	1 day; 1 cohort

We have conducted over 200 ethnobridging studies since 2004, and offer two potential solutions, both of which decrease development time and increase asset value:

- A single study in the U.S. once the target doses for the global study have been identified
- The addition of Asian study participants to FIH studies being conducted in the U.S.

We recruit from a large ethnic population, and have a dedicated, multilingual Asian recruitment and outreach department to liaise with our participants.

Altasciences conducted the largest ethnobridging study ever performed, which led to a label change stating that Asians needed to be administered a half-dose of this particular medication, as opposed to Caucasians.

Altasciences' operational highlights:

- Recruit an average of ~750 Asian participants yearly
- Have over 9,000 Asian participants in our database
- Multilingual recruiting, marketing, and clinical operations staff

REFERENCE

1 Lo C, Nguyen S, Yang C. Pharmacogenomics in Asian Subpopulations and Impacts on Commonly Prescribed Medications. Clinical and Translational Science, February 2020. https://ascpt.onlinelibrary.wiley.com/doi/full/10.1111/cts.12771 accessed May 11, 2022.

2 Asano K, Aoi Y, Kamada S et al. Points to Consider for Implementation of the ICH E17 Guideline: Learning from Past Multiregional Clinical Trials in Japan. Clin Pharm and Thera, November 2020. https://doi.org/10.1002/cpt.2121 accessed May 25, 2022.

ALTASCIENCES' RESOURCES

Webpage

Supporting Global Drug Submissions with Ethnobridging

Blog

Protocol Design Concepts in Phase I Ethnobridging Clinical Trials

Ethnobridging Supports Global Clinical Development

Fact Sheet

Ethnobridging Clinical Research Capabilities

Webinar

Ethnobridging in Phase I Clinical Trials

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 30 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.