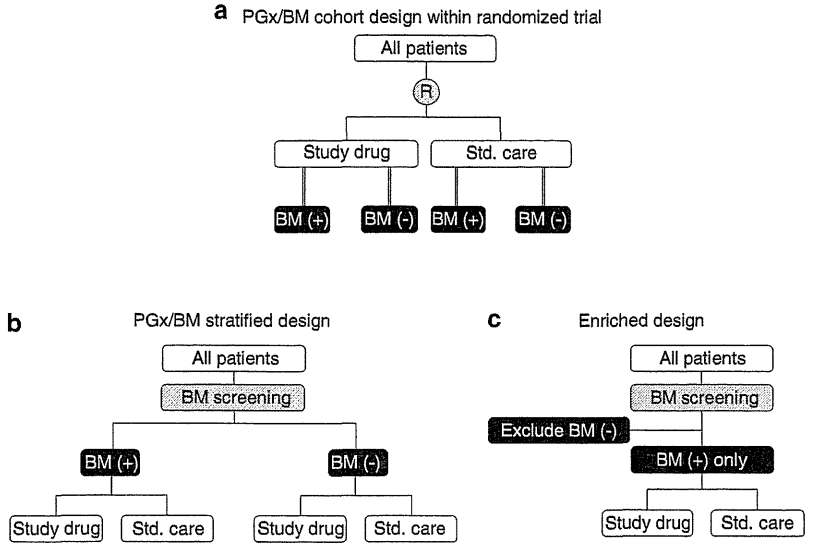

Figure1 Common study designs used in clinical trials utilizing pharmacogenomics (PGx) or biomarker (BM). (**a**) Design where the randomization is independent of the results of the PGx/BM screening. (**b**, **c**) Design where the randomization is performed by the results of the PGx/BM screening. R, randomization; Std. care, standard of care, BM (+), PGx/BM test positive population; BM (−), PGx/BM test negative population.

first category is 'PGx/BM cohort design', where the randomization was independent of the results of the PGx/BM screening. The second and third categories are 'PGx/BM stratified design' and 'enriched design', where the randomization was carried out using the results of the PGx/BM screening. The difference between the second and third categories is whether patients without the target PGx/BM (PGx/BM(-)) were included ('PGx/BM stratified design') or excluded ('Enriched design') in the clinical trial. An orphan status designation, based on the information available in the public database (http://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/orphan_drug.html), was also included as a factor in our analysis, because characteristic differences in the design of clinical trials of orphan and non-orphan drugs (for example, randomization) have been reported previously.[16] The information of the feature in the key trials described above was collected independently by us and differences were reconciled by consensus.

RESULTS

Among the 52 selected NDAs, 29 NDAs (55.8%) contained 58 PGx/BM-guided key trials. Of these 29 NDAs, 8 NDAs also contained key trials without utilizing PGx/BM. Figure 2 shows BMs that were targeted in the PGx/BM-guided key clinical trials and clearly indicates that the epidermal growth factor receptor (EGFR), *Bcr-Abl* and vascular endothelial growth factor were the major targets for drug development in oncology.

Table 1 summarizes the design features of key trials according to the PGx/BM utilization. Fifty-eight PGx/BM-guided trials were classified into 39 'PGx/BM cohort design' and 26 'Enriched design'. Seven trials were classified into both categories because they were enriched based on one BM and another BM was used for conducting the exploratory analysis. In this study, none of the trials could be classified under the 'PGx/BM stratified design' category.

The main objective of the trials with the 'PGx/BM cohort design' was to conduct exploratory analysis on the clinical relevance of the targeted PGx/BM (for example, *Bcr-Abl*, *c-Kit*, EGFR expression, kirsten rat sarcoma viral oncogene homolog (KRAS), β2-microglobulin (MG), phosphatase and tensin homolog deleted from chromosome-10 (PTEN) and vascular endothelial growth factor) in terms of drug efficacy or acquisition of resistance against a drug. Additionally, relationship between the BM (α1-MG, β2-MG and N-acetylglucosaminidase) and drug-induced renal injury was

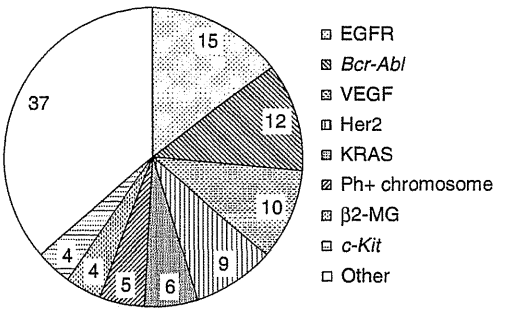

Figure2 Target of pharmacogenomics(PGx)/biomarker(BM)-guided key trials. The numerical value shows number of PGx/BM-guided key trials targeting a particular PGx/BM. In a decreasing order of the number, major BMs targeted in the key trial were epidermal growth factor receptor (EGFR), *Bcr-Abl*, vascular endothelial growth factor (VEGF), human EGFR related 2 (Her2), kirsten rat sarcoma viral oncogene homolog (KRAS), Philadelphia chromosome (Ph+ chromosome), β2-microglobulin (β2-MG) and *c-Kit*. BMs counted <4 were as follows; cluster of differentiation (CD) 20 ($n=3$), echinoderm microtubule associated protein-like 4—anaplastic lymphoma kinase (EML4-ALK), estrogen receptor (ER), extracellular signal-regulated kinase (ERK) and phosphatase and tensin homolog deleted from chromosome-10 (PTEN) ($n=2$), acyl-CoA thioesterase 9 (ACOT9), CC chemokine receptor 4 (CCR4), *c-Met, Crk, Ddx5,* deletion 5q cytogenetic abnormality, deoxycytidine kinase (dCK), excision repair cross-complementing 1 (ERCC1), *FLK31079*, folylpoly-γ-glutamate synthetase (FPGS), *Grb7*, hepatocyte growth factor (HGF), hypoxia inducible factor-1α (HIF-1α), human equilibrative nucleoside transporter (hENT1), insulin-like growth factor receptor 1 (IGF1R), international normalized ratio (INR), multidrug resistance protein 5 (MRP5), *N*-acetylglucosaminidase (NAG), $p95^{HER2}$, phosphoinositide-3-kinase, catalytic, alpha polypeptie (PIK3CA), Ras p21, ribonucleotide reductase M1 (RRM1), thymidylate synthase (TS), von Hippel-Lindau (VHL), α1-MG and γ-glutamyl hydrolase (GGH) ($n=1$).

Table1 Characteristics of key trials of anti-cancer drugs

	Number (%)	
Characteristics	*PGx/BM-guided trial* (n = *58*)	*Trial without PGx/BM use* (n = *50*)
Randomized	35 (60.3)	30 (60.0)
Blinding		
Double-blind	13 (22.4)	13 (26.0)
Single-blind	0	2 (4.0)
Open-label	45 (77.6)	35 (70.0)
Comparator		
Active	21 (36.2)	19 (38.0)
Supportive care	5 (8.6)	0
Placebo	9 (15.5)	11 (22.0)
None	23 (39.7)	20 (40.0)
Primary trial end point reported		
Disease response	30 (51.7)	24 (48.0)
Time to event (survival or disease progression)	28 (48.3)	26 (52.0)
Study design		
PGx/BM cohort	39 (67.2)[a]	—
PGx/BM stratified	0	—
Enriched	26 (44.8)[a]	—
Location		
Japan	15 (25.9)	15 (30.0)
Multi-region including Japan	7 (12.1)	6 (12.0)
Without Japan	36 (62.1)	29 (58.0)
Orphan	21 (36.2)	18 (36.0)
Non-orphan	37 (63.8)	32 (64.0)

Abbreviations: BM, biomarker; PGx, pharmacogenomics.
[a]Seven trials were classified as both of PGx/BM and enriched design.

evaluated in the clinical trials of Azacitidine for the myelodysplastic syndrome. In the randomized clinical trials of Erlotinib for non-small cell lung cancer, EGFR expression level was one of the factors for patient allocation in each arm.[17] In the clinical trials of Gefitinib for non-small cell lung cancer, the efficacy was retrospectively analyzed in stratified population according to types of specific *EGFR* mutations.[18]

The main objective of the trials with 'enriched design' was to stratify the population, which more likely will have a favorable response to a drug. Targeted BMs in the trials under this category were CC chemokine receptor 4, cluster of differentiation 20, deletion 5q cytogenetic abnormality, echinoderm microtubule associated protein-like 4-anaplastic lymphoma kinase, EGFR, estrogen receptor, human EGFR related 2 and Philadelphia chromosome. There are probably at least two justifications for the selection of enriched design: approaches involving pharmacological profiling, as well as approaches involving pathological profiling. As for examples we could mention the use of monoclonal antibody against the targeted BM (such as Mogamulizumab, a humanized immunoglobulin G_1 monoclonal antibody against CC chemokine receptor 4 and Cetuximab, a chimeric immunoglobulin G_1 monoclonal antibody against EGFR) for the pharmacological approach, and also the use of low molecular compound against the targeted BM (such as Dasatinib, which inhibits kinases derived from Philadelphia chromosome in acute lymphatic leukemia) for the pathological approach.

Regarding the orphan drug designation, 32.7% (17/52) of the anti-cancer drugs, which included 39 key trials, was designated as orphan drugs. Randomized design was less represented in the key trials for the orphan drugs (14/39, 35.9%) than for the non-orphan drugs (51/69, 73.9%), and the PGx/BM-guided trials showed no clear relationship between the orphan (21/39, 53.8%) and non-orphan drugs (37/69, 53.6%). Disease response as a primary end point was more common in the key trials for the orphan drugs (30/39, 77.0%) than for the non-orphan drugs (24/69, 34.8%).

For the other factors, ~60% of the key trials were conducted as randomized trial, ~70–80% of which were non-blinded trials. Actually, ~40% of the key trials were conducted without any comparator. Time to event was set in about half of the key trials. Only about 25–30% of the key trials were conducted as local trials in Japan and 60% of the key trials were conducted outside of Japan. There were, however, no major differences between the key trials performed with and without the utilization of PGx/BM.

DISCUSSION

This study reveals that the development of nearly half of the approved drugs in oncology was based on PGx/BM-guided trials, suggesting that PGx/BM is commonly utilized in the clinical trials in oncology. The targeted PGx/BM mostly used in the trial was for evaluating the efficacy of a drug, although some BM, such as β2-MG and *N*-acetylglucosaminidase, were used for safety evaluation.

More than half of the PGx/BM-guided key trials were classified as 'PGx/BM cohort design'. Although we commonly found trials also under the 'enriched design' category, no trials were found under the 'PGx/BM stratified design' category. This observation suggests that exploratory application of PGx/BM for evaluating a relationship with drug response (efficacy/safety) is still a major factor in the oncology trials. Although the PGx/BM cohort design is suitable for establishing a hypothesis by analyzing stored samples (for example, DNA), its limitation in data evaluation, such as statistical bias, should be recognized.[5,19] In our recent publication,[5] we have listed five points (such as sample collection for future use and BM qualification) as the remaining challenges in the PGx-guided drug development. To conduct a PGx/BM Cohort study properly, it is very important to consider how to collect samples from clinical trials and store them. Qualification of BM by a regulatory agency is also a key to promote the utilization of PGx/BM in clinical trials in oncology. If more PGx/BM were discovered and qualified, more PGx/BM-guided trials could be conducted. Enriched design may improve an efficiency of drug development by selecting patients who are likely to better respond to a drug, selection of which was based on the response of the candidate PGx/BM to the drug;[14] however, application of this approach has also a limitation because it could not provide a benefit/risk profile in PGx/BM off-target population due to the lack of scientific data. In general, for accumulating strong evidences on the contribution of PGx/BM to drug response, PGx/BM stratified design should be adopted, because this design has been recognized as the gold standard design that could provide evidences for data evaluation.[5,15] Therefore, usefulness and limitation of each design should be thoroughly considered in planning a PGx/BM-guided trial. These data indicate that five challenges described in our recent manuscript are also applicable in oncology.[5]

In this study, orphan designation did not affect the utilization of PGx/BM in the key trial, while drugs designated as the orphan drugs

have been approved on the basis of relatively limited clinical evidence, such as less randomized trials as recently reported.[16,20] To promote drug development in orphan disease, advances in science, such as elucidation of the disease mechanism and discovery/qualification of new PGx/BM in orphan disease, are necessary.[5] Therefore, more research on PGx/BM is encouraged in the case of orphan diseases. In cases where the scientific data on PGx/BM is limited, PGx/BM cohort design may be useful in discovering new hypothesis on the relationship between PGx/BM and drug response. More applications of PGx/BM in clinical trials of orphan diseases may help in identifying a target population and providing more clear evidence on drug responses even in a stratified small population.

As drug development process has become more globalized, data obtained in a foreign country are frequently included in the common technical document used for NDA. Our study shows that ~60% of the key trials are actually conducted outside Japan. Although percentage of trial sites caused no major differences between the key trials performed with and without the use of PGx/BM, more trials involving PGx/BM are needed to be performed in Japan. Recently in Japan, the number of approved drugs, whose approval was based on data obtained from the multi-regional clinical trials (MRCTs), has also increased.[21] Application of PGx/BM in multi-regional clinical trials is encouraged for accumulating more information, for it might contribute to a better understanding about the effects of ethnic factors on drug responses.[5] Furthermore, in recent years, draft guidelines focusing on methodological issues using PGx/BM in clinical trials (such as patient selection and enrichment strategy) have been published independently by the European Medicines Agency and US Food and Drug Administration[22,23] All regulatory agencies (European Medicines Agency, Food and Drug Administration and Pharmaceuticals and Medical Devices Agency) in the international conferences on harmonization (ICH) recognize the importance of PGx/BM in clinical trials and encourage the application of PGx/BM in drug development.[2] For promoting the appropriate application of PGx/BM in clinical trials in the era of globalization, establishment of an international guideline would be important. Thus, regulatory collaborations should be further reinforced.

In conclusion, PGx/BM was commonly utilized in the key trials to provide evidences for regulatory approval of anti-cancer drugs in Japan. However, most of these trials were exploratory rather than confirmatory. More researches, such as discovery/qualification of new BMs, are necessary to further promote the application of PGx/BM in oncology. Common understandings regarding the design of PGx/BM-guided trials, in terms of usefulness and limitation, will contribute to provide better evidences in PGx/BM-guided clinical trials. In the era of globalization of drug development, establishment of an international guideline and close collaboration among regulatory agencies are necessary to promote appropriate application of PGx/BM in clinical trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Significant Differences in Drug Lag in Clinical Development Among Various Strategies Used for Regulatory Submissions in Japan

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Although the number of global clinical trials (GCTs) conducted in multiple countries including Japan has increased recently, it is not clear how much these GCTs help in reducing the lag in drug development (LDD: difference between the submission dates for new drug applications (NDAs) in the United States and Japan). We examined the effects of various clinical development strategies on LDD because the development period depends on what types of clinical trials were conducted for the Japanese NDA. Although various drug development strategies are available, deciding early on an appropriate strategy is a key to minimizing the LDD in Japan. The inclusion of GCTs in the clinical development strategy is also important; simultaneously, the smaller sample size of the Japanese population should be taken into consideration. Furthermore, reinforcement of Japan's capability to lead drug development may also be important in providing innovative drugs to Japanese patients without any significant LDD.

Japan has struggled for many years with the so-called "drug lag," a lag in drug approval times as compared with those in the United States and the European Union.[1] This is due to a lag in the regulatory review after the new drug application (NDA) is submitted to the Pharmaceuticals and Medical Devices Agency (PMDA: the Japanese regulatory agency) and also due to a lag in drug development (LDD), which is mainly a result of delays in or longer periods for clinical development in Japan. To resolve this drug lag problem, the Japanese government has taken several measures, such as increasing the number of reviewers in the PMDA, establishing core clinical research centers, and establishing regulatory guidelines promoting the active contribution of Japan to global drug development.[2–8] With these efforts, the drug lag has gradually decreased in recent years. In particular, the lag in the regulatory review dramatically decreased from 1.2 years in fiscal year (FY) 2006 to 0.1 year in FY2010, although the LDD remained at 1.0 year in FY2010 and did not show any tendency for improvement over these years.[7] Therefore, the current major task that remains to be resolved is how to decrease the LDD in Japan. In this regard, a guideline focusing on global clinical trials (GCTs), titled "Basic Principles on Global Clinical Trials," was published in 2007[4] with the aim of synchronizing the rate of clinical development in Japan with that in the United States and the European Union and substantially reducing the lag. However, it is not clear how much GCTs actually contribute to the decrease in the LDD because the drug development period largely depends on the type of clinical trials conducted before the submission of NDAs in Japan.[9]

We examined the relationship between the clinical development strategies (CDSs) and the LDD to identify an appropriate strategy for NDA submission in Japan. We also discuss ways to decrease the LDD with respect to the factors identified in this analysis.

RESULTS

From FY2007 to FY2012, 218 drugs representing new molecular entities were approved in Japan. Of these 218 drugs, 183 were selected for the analysis; among the rest, 21 were excluded because they were approved only in Japan and were not developed in the United States, 10 were excluded because the submission dates of their NDAs to the US Food and Drug Administration (FDA) were not available, and 4 were excluded because they were biosimilar drugs (approved as a new molecular entity at that time). Characteristics of the 183 selected drugs are summarized in **Table 1**. As indicated in **Table 1**, CDSs were classified as "Local trial" for 69 drugs, "Local and foreign trials"

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for 59 drugs, "Bridging study" for 19 drugs, "Global clinical trial" for 18 drugs, "Foreign trial" for 13 drugs, and "No efficacy/safety trial" for 5 drugs. Of these, only 19% (34 drugs) were approved first in Japan. Major therapeutic areas covered by these drugs were L (antineoplastic and immunomodulating agents: 21%), N (nervous system: 16%), A (alimentary tract and metabolism: 15%), and J (anti-infectives for systemic use: 13%). No differences were seen in the "year of approval in Japan." With regard to the category of originator and marketing authorization holder (MAH), 39% were developed by Japanese enterprises, but only 12% of the total were self-developed (of Japanese origin).

Figure 1 shows the LDD between the United States and Japan for different CDSs that were used for NDA submissions in Japan. The median value for all cases (n = 183) was 1,111 days. As compared with this median value, the LDD was significantly shorter for the "Global clinical trial" (median = 90 days) and "Foreign trial" (median = 560 days) categories but longer for the "Local trial" (median = 1,870 days) category. A relatively longer lag was also observed for the "No efficacy/safety trial" category, although this category included only special cases (for example, the feasibility of conducting clinical trials for a drug for reducing radiation exposure in the body is very low in Japan).

As shown in **Figure 2**, the LDD was also different for different target therapeutic areas, which were categorized according to the Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization. The LDD was significantly shorter for L (antineoplastic and immunomodulating agents, median = 778 days, n = 38) but was longer for N (nervous system, median = 2,725 days, n = 30). The LDDs of C (cardiovascular system, median = 710 days, n = 8), J (anti-infectives for systemic use, median = 613 days, n = 23), and R (respiratory system, median = 733 days, n = 8) also had relatively shorter median values, although large variability was observed in these therapeutic areas. Regarding CDSs based on therapeutic areas, the "Global clinical trial" category was mainly found under L (antineoplastic and immunomodulating agents, 8/18 cases). Neither "Global clinical trial" nor "Foreign trial" was found under C (cardiovascular system) or N (nervous system), even though the LDD was relatively shorter for the C (cardiovascular system) and longer for the N (nervous system) (see **Supplementary Table S1** online) categories.

Another important factor causing the LDD could be the starting time for the clinical trial. Therefore, we analyzed whether the starting time for the phase II trial in Japan (phase III trial timing was used for cases without the phase II trial) occurred before the submission of the NDA to the FDA or not. As shown in **Figure 3**, the median value of LDD was significantly lower for all CDSs for which the clinical trial in Japan began before the NDA was submitted to the FDA ($P < 0.01$): 0 vs. 3,023 days for "Local trial," 637 vs. 1,856 days for "Local and foreign trials," 231 vs. 1,866 days for "Bridging study," and 84 vs. 1,162 days for "Global clinical trial." It is noteworthy that, even in the case of CDSs for which the clinical trial in Japan started after the NDA submission to the United States, the LDDs for "Local and foreign trials," "Bridging study," and "Global clinical trial" were significantly

Table 1 Summary of analyzed drugs

	Number of drugs (n = 183; %)
Clinical development strategy for NDA submission in Japan	
Local trial	69 (38%)
Local and foreign trials	59 (32%)
Bridging study	19 (10%)
Global clinical trial	18 (10%)
Foreign trial	13 (7%)
No efficacy/safety trial	5 (3%)
Time of approval	
First in Japan	34 (19%)
First in the United States	149 (81%)
Year of approval in Japan	
FY2007	32 (17%)
FY2008	27 (15%)
FY2009	21 (11%)
FY2010	33 (18%)
FY2011	37 (20%)
FY2012	33 (18%)
Therapeutic area (ATC classification)	
A (Alimentary tract and metabolism)	27 (15%)
B (Blood and blood-forming organs)	13 (7%)
C (Cardiovascular system)	8 (4%)
D (Dermatologicals)	2 (1%)
G (Genitourinary system and sex hormones)	6 (3%)
H (Systemic hormonal preparations)	5 (3%)
J (Anti-infectives for systemic use)	23 (13%)
L (Antineoplastic and immunomodulating agents)	38 (21%)
M (Musculoskeletal system)	3 (2%)
N (Nervous system)	30 (16%)
P (Antiparasitic products, insecticides, and repellents)	1 (1%)
R (Respiratory system)	8 (4%)
S (Sensory organs)	9 (5%)
V (Various)	10 (5%)
Characteristics of originator and marketing authorization holder	
Japanese enterprise	72 (39%)
Self-developed by Japanese enterprise	23 (12%)
Licensed-in for development by Japanese enterprise	49 (27%)
Non-Japanese enterprise	111 (61%)
Self-developed by non-Japanese enterprise	82 (45%)
Licensed-in for development by non-Japanese enterprise	29 (16%)

ATC, Anatomical Therapeutic Chemical classification; FY, fiscal year; NDA, new drug application.

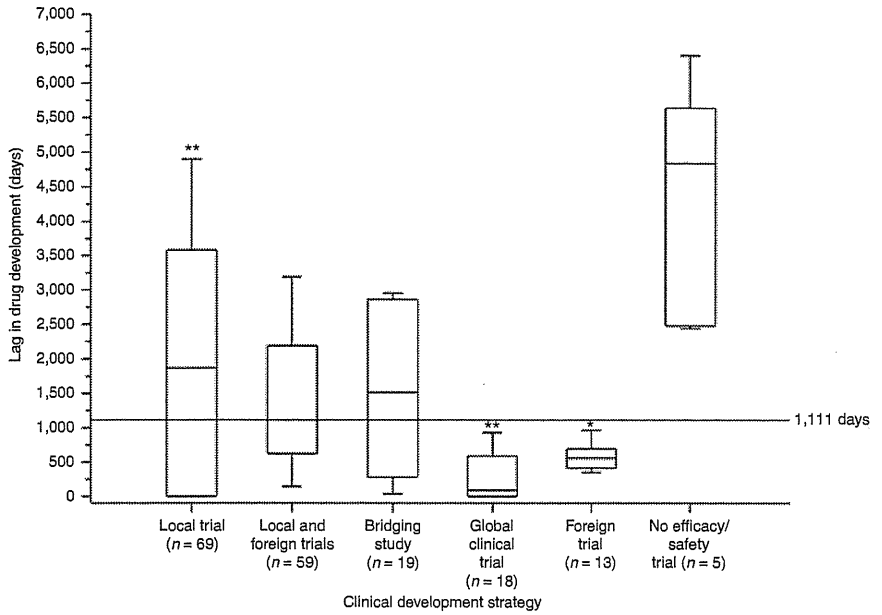

Figure 1 Lag in drug development (LDD) for different clinical development strategies used for submission of NDAs in Japan. The LDD is shown for each indicated clinical development strategy. In this box plot, the top, the middle, and the bottom represent the 75th percentile, the median, and the 25th percentile, respectively. Error bars represent the 90th and the 10th percentiles. For analysis, each category was compared with the median LDD value (1,111 days) by using the Wilcoxon signed-rank test. $^{*}P < 0.05$. $^{**}P < 0.01$.

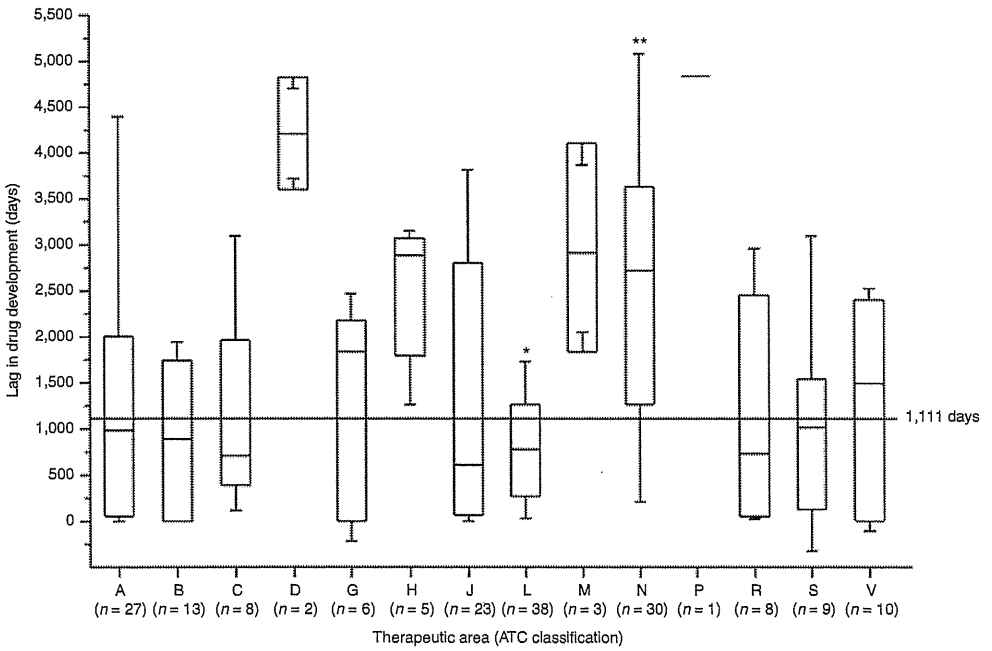

Figure 2 Lag in drug development (LDD) in each therapeutic area. LDDs, categorized according to the Anatomical Therapeutic Chemical (ATC) classification, are shown for the following therapeutic areas: (A) alimentary tract and metabolism ($n = 27$), (B) blood and blood-forming organs ($n = 13$), (C) cardiovascular system ($n = 8$), (D) dermatologicals ($n = 2$), (G) genitourinary system and sex hormones ($n = 6$), (H) systemic hormonal preparations ($n = 5$), (J) anti-infectives for systemic use ($n = 23$), (L) antineoplastic and immunomodulating agents ($n = 38$), (M) musculoskeletal system ($n = 3$), (N) nervous system ($n = 30$), (P) antiparasitic products, insecticides, and repellents ($n = 1$), (R) respiratory system ($n = 8$), (S) sensory organs ($n = 9$), and (V) various ($n = 10$). In this box plot, the top, the middle, and the bottom represent the 75th percentile, the median, and the 25th percentile, respectively. Error bars represent the 90th and the 10th percentiles. For analysis, each category was compared with the median LDD value (1,111 days) by using the Wilcoxon signed-rank test. $^{*}P < 0.05$. $^{**}P < 0.01$.

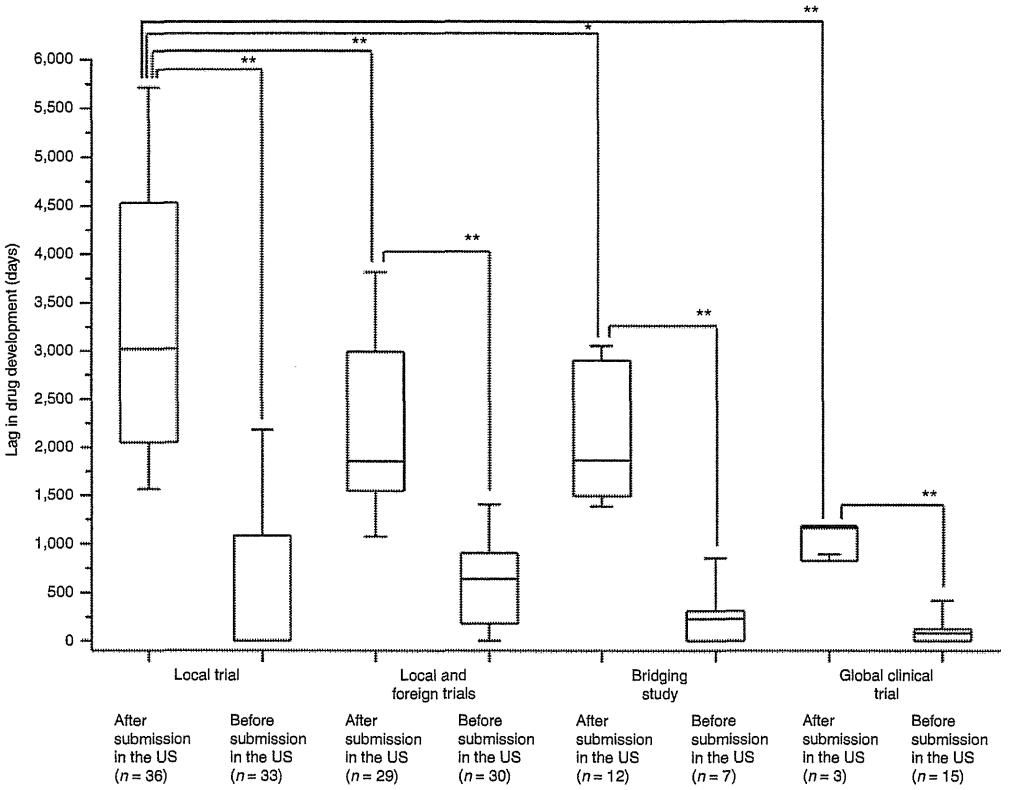

Figure 3 Effects of timing of initiation of the phase II clinical trial in Japan on the lag in drug development (LDD). The LDD was compared for the clinical development strategy and timing of initiation of the phase II clinical trial in Japan before or after the submission of the new drug application (NDA) in the United States. In this box plot, the top, the middle, and the bottom represent the 75th percentile, the median, and the 25th percentile, respectively. Error bars represent the 90th and the 10th percentiles. For analysis, data for the after-submission stage in each category were compared with those for the "Local trial" by using the Wilcoxon rank-sum test. For each strategy, comparison was carried out between the data for the stages before and after NDA submission. *$P < 0.05$. **$P < 0.01$.

shorter than that for "Local trial." In fact, in such GCTs, two of three trials were conducted only in the Asian region.

We further examined the relationship between the types of originator/MAH and the LDD. **Figure 4** shows the results of analysis of LDDs based on the type of MAH (based in Japan or not) and origin of the drug (self-developed/licensed-in). The LDD was significantly shorter for the "Self-developed drug by Japanese enterprise" (median = 0 day, $n = 23$, $P < 0.01$) but longer for the "Licensed-in drug by Japanese enterprise" (median = 2,380 days, $n = 49$, $P < 0.01$). In fact, 17 of 23 NDAs for "Self-developed drugs by Japanese enterprise" were submitted first in Japan, but only 3 of the 17 were approved in the United States.

Figure 5 shows the relationship between the type of CDS and the sample size of the Japanese population in clinical trials. The percentage of Japanese subjects among total subjects (median) was 13% for "Local and foreign trials," 16% for "Bridging study," 11% for "Global clinical trial," and 0% for "Foreign trial." These percentages were significantly lower than that for "Local trial." It should be noted that the percentage for "Global clinical trial" ($n = 18$) varied depending on which operational regions were included in the trial, and the value was higher in Asian GCTs (median = 41%, $n = 6$) than in other GCTs (median = 10%, $n = 12$).

DISCUSSION

Our analysis clearly demonstrated that the LDD was markedly shorter in the CDS of "Global clinical trial," suggesting that including Japan while conducting GCTs could decrease the LDD, which in turn could eliminate the "drug lag." Although "Foreign trial" also showed a shorter lag, it mainly included drugs for orphan diseases, such as human immunodeficiency virus infection, suggesting that the CDS of "Foreign trial" is applicable to only a limited number of cases in Japan. It should be noted that the median LDD for all cases was 1,111 days, and this did not decrease between FY2007 and FY2012. Although this LDD value was relatively longer than the previously reported value of 12–20 months,[7,10] it could have resulted from the differences in the scope of target drugs (only new molecular entities for all therapeutic areas were considered in this analysis but not in the other published reports) and the target years (data up to FY2012 were included in this analysis but not in the other published reports) considered for analysis. In any case, these results indicated that the LDD is still a serious issue in Japan that needs to be resolved. The number of GCTs included in this analysis is still limited but has recently increased.[11] Earlier consideration of CDS and further improvement of clinical trial environment in Japan may promote more active participation of Japan in GCTs.

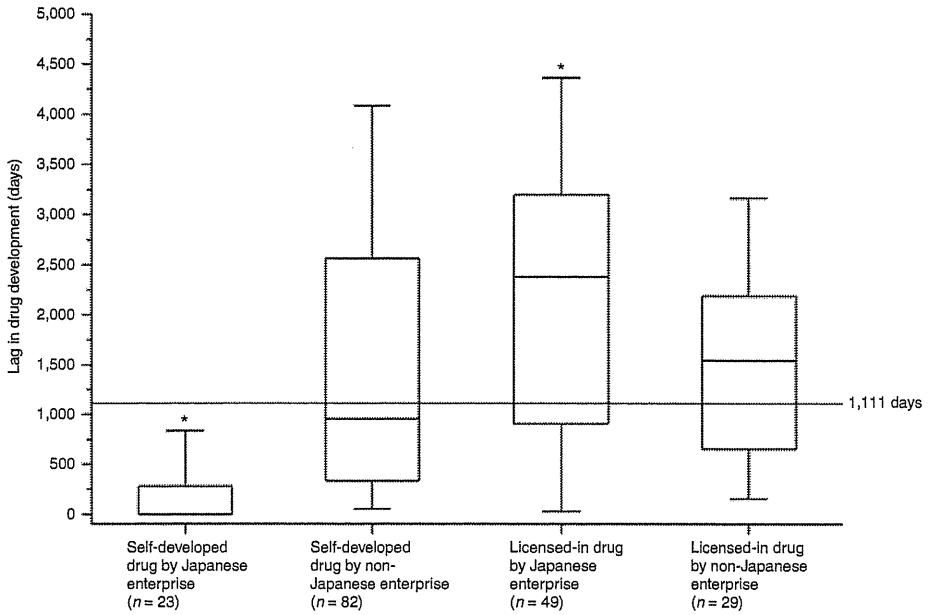

Figure 4 Relationship between the originator/marketing authorization holder of a drug and lag in drug development (LDD). The LDD was analyzed on the basis of various types of originator and marketing authorization holder of a drug. In this box plot, the top, the middle, and the bottom represent the 75th percentile, the median, and the 25th percentile, respectively. Error bars represent the 90th and the 10th percentiles. For analysis, each category was compared with the median LDD value (1,111 days) by using the Wilcoxon signed-rank test. *$P < 0.01$.

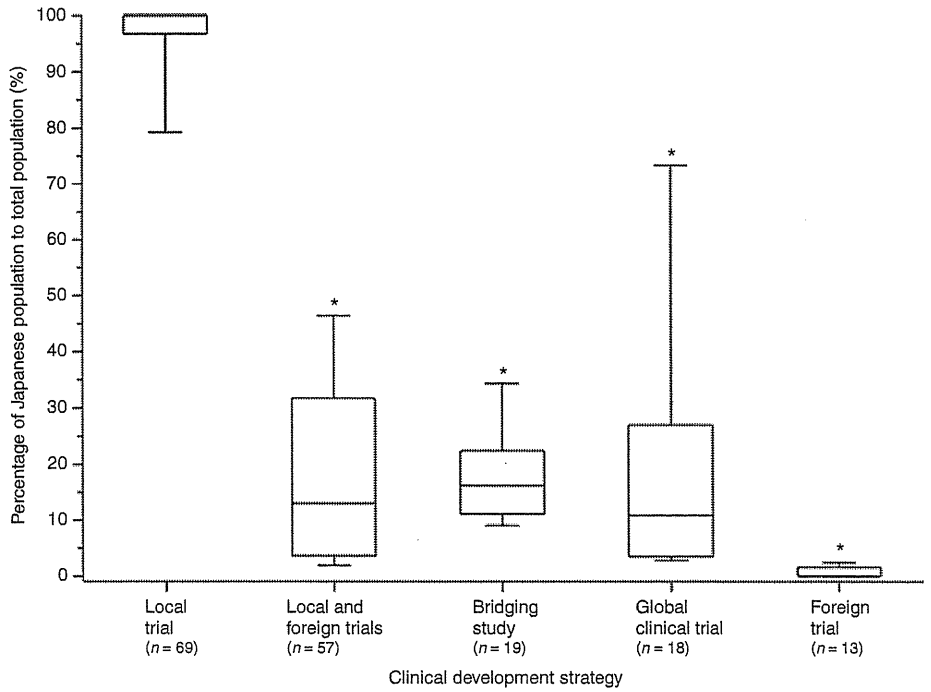

Figure 5 Ratio of Japanese to total subjects in efficacy/safety evaluation trials. The ratio between Japanese patients and total patients in the efficacy/safety clinical trials is shown in terms of percentage value for each category. In this box plot, the top, the middle, and the bottom represent the 75th percentile, the median, and the 25th percentile, respectively. Error bars represent the 90th and the 10th percentiles. For analysis, each category was compared with the "Local trial" category by using the Wilcoxon rank-sum test. *$P < 0.01$.

In this analysis, we identified four factors (including CDS) that affected the LDD, and they should be considered when looking for an appropriate strategy for drug development. One of these factors is the therapeutic area of drug development. It is noteworthy that the lag varied depending on the target therapeutic area and was significantly longer for the nervous system (N category in the ATC classification). It may be possible that the situation in the N therapeutic area could be improved by

conducting GCTs because no GCTs were carried out for drugs of the N category that were included for the analysis. In fact, significantly shorter lag and higher percentage of GCTs were observed for drugs of the L group (antineoplastic and immunomodulating agents), and 28 of 38 drugs in this category were anticancer drugs. In 2006, the anticancer drug category was recognized as a typical area in which LDD was observed.[12] A guidance, titled "Clinical Evaluation of Anti-Oncology Drugs," published in 2005, might have contributed to improving the situation even in part, by facilitating the means to conduct GCTs in anticancer drug development through the promotion of international harmonization on regulatory requirements such as the end point, which has long been considered a hurdle in conducting GCTs.[13] Therefore, establishing a guidance that would encourage international harmonization on clinical evaluation may be useful in further promoting GCTs in other therapeutic areas. In some therapeutic areas, such as cardiovascular system (C category in the ATC classification), the LDD was relatively shorter even though GCTs were not conducted. This could be due to higher feasibility of conducting local clinical trials because of the availability of larger numbers of Japanese patients with the disease. Therefore, "Local trial" as a CDS could also be a useful strategy to consider when patient enrollment can be achieved as speedily as the "Global clinical trial." Further improvement in clinical trial site, such as including human resources in Japan, will be necessary to shorten the duration of the trial period, as was recently reported.[14]

Another factor is the timing of initiation of a clinical trial in Japan. As shown in **Figure 3**, the lag was shorter when the phase II clinical trial in Japan started before the NDA was submitted to the United States. The timing of initiation of drug development has been reported as a factor that causes the drug lag.[10] Our analysis revealed that the LDD was significantly shorter in all types of CDSs in which clinical trials in Japan were started before the NDAs were submitted in the United States. This result suggests that the timing of initiation of a clinical trial in Japan is probably more important than the strategy chosen for the clinical development. In addition, the "Global clinical trial" CDS could be an effective strategy even when the starting time of clinical development was delayed in Japan (e.g., Japan could not participate in the clinical trial for NDA submission to the United States) because the LDD for the "Global clinical trial" CDS was the shortest among cases in which the clinical trial in Japan began after the NDA submission in the United States.

In considering the start time for a clinical trial in Japan, the relationship between the originator and MAH of a drug seems to be important because the LDD was significantly shorter for the "Self-developed drug by Japanese enterprise" and longer for the "Licensed-in drug by Japanese enterprise" categories. For a "self-developed drug," the lag time was 0 days (median) for a Japanese enterprise, but the lag was 954 days (median) for a non-Japanese enterprise. It has been reported that the country that houses the headquarters of a pharmaceutical enterprise is usually given priority for developing a drug.[15] Thus, to facilitate faster access of a new drug to Japanese patients, it is very important to reinforce Japan's capability to lead drug development, including discovering a new candidate drug. Earlier communication with the PMDA may help to resolve issues regarding clinical development in Japan and promote the establishment of an appropriate drug development strategy as soon as possible by promoting a better relationship between the originator and the MAH.

As described above, inclusion of GCTs in CDS can lead to a decrease in the LDD. However, for successful drug development, one should also consider how much data on the Japanese population could be accumulated by the time of the NDA submission in Japan.[11] If an NDA based on a CDS were not approved in Japan, such a CDS would not be appropriate even in the case of no LDD. Our analysis clearly showed that the percentage of Japanese people was markedly lower for the "Local and foreign trials," "Bridging study," "Global clinical trial," and "Foreign trial" categories than that for the "Local trial" category. The smaller sample size of the Japanese population could be a limitation factor for data evaluation, particularly for drug safety evaluation. In the case of a GCT, sufficient Japanese subjects should be enrolled as often as possible to examine the consistency of results obtained between Japanese and overall populations.[4,6] Intensive postmarketing studies (e.g., evaluating safety in Japanese patients) may be necessary, particularly when data accumulated on Japanese population are very limited at the time of drug approval. It should be noted that the percentage of Japanese population in the case of the "Global clinical trial" category varied greatly. The percentage of Japanese patients in the Asian GCTs was higher than that in the "Bridging study" category and non-Asian GCTs. This result suggested that even when the CDS of "Global clinical trial" is considered, Asian GCTs have more opportunity to include sufficient Japanese patients than non-Asian GCTs, enabling data accumulation without a major decrease in the Japanese sample size.

Finally, our analysis has some limitations. First, the LDD for new molecular entity drugs approved in Japan was compared only with that for drugs approved in the United States. Second, the LDD for drugs not approved in the United States was assumed to be zero. Thus, the situation may differ when comparing with other countries and when a drug currently not approved in the United States actually becomes approved in the United States in the future.

In conclusion, although various drug development strategies (such as Local/foreign clinical trial, Bridging study, and Global clinical trial) are available, deciding early on an appropriate strategy is a key to minimizing the LDD in Japan. Particularly, a proactive approach should be taken to conduct GCTs, especially in therapeutic areas for which the feasibility of conducting a local clinical trial is low. Furthermore, reinforcement of Japan's capability to lead drug development, including discovering new candidate drugs, may also be important in providing innovative drugs to Japanese patients without any significant LDD. Finally, CDSs may be more diversified in the future as personalized drugs targeting narrow populations increase because development strategy not only for a drug but also for companion diagnostics should be considered. More discussion and international harmonization on regulatory requirements for drug approval, including approval of companion diagnostics, will be

necessary to minimize the barriers to eliminating LDD in future drug development.

MATERIALS AND METHODS

Data source and collected information. We searched a publicly available database for approved drugs in Japan (http://www.info.pmda.go.jp/approvalSrch/PharmacySrchInit?) and identified drugs that were approved in Japan as new molecular entities between FY2007 and FY2012 (April 2007–March 2013). We then collected various types of information on these drugs from the following sources for analysis: PMDA website (http://www.pmda.go.jp/), FDA website (http://www.fda.gov/), the Federal Register (https://www.federalregister.gov/), the World Health Organization ATC/DDD (defined daily dose) index (http://www.whocc.no/atc_ddd_index/), and websites of pharmaceutical companies. Data collected from these sources included nonproprietary/proprietary name, NDA submission/approval dates in Japan and the United States, types of MAH (Japan-based enterprise or not), target therapeutic area (categorized based on World Health Organization ATC classification), and subject number in each trial. If an NDA submission/approval date was not available in the sources described above, published articles were used instead.[16–19] The NDA submission date was defined as the date on which the NDA was accepted by the regulatory agency (the PMDA or the FDA). A commercially available database, "Asuno Shin-Yaku" by Technomics (https://technomics-info.com/), was used to collect information regarding the origin of drugs (self-developed/licensed-in drugs) and progress of clinical development in Japan and the United States. Any investigational active substance that was originally discovered by a MAH was categorized as a "self-developed drug," and any other drug was categorized as a "licensed-in drug." Information on clinical development status in the United States (ongoing, suspended, or no development) and on the starting date of phase II trials in Japan (a phase III trial start time was used for studies without a phase II study), as an index for actual initiation of clinical development in patients with a target disease, was also collected. Drugs that were not approved in the United States and for which no development plans existed in the United States were excluded from the analysis because they were developed only in Japan and, therefore, their inclusion in this analysis might have led to misinterpretation of results.

For the analysis, all data were collected between 23 July 2013 and 2 August 2013. In this retrospective analysis, the number of cases was counted based on a drug's review report; thus, if two or more formulations

Table 2 Classification of clinical development strategy for NDA submission in Japan

	Clinical development strategy	Key clinical trial					
		Local trial		Foreign trial		Global clinical trial	
		Exploratory	Confirmatory	Exploratory	Confirmatory	Exploratory	Confirmatory
1	"Local trial"	O	O	–	×	×	×
2		×	O	–	×	×	×
3		O	×	×	×	×	×
4	"Local and foreign trials"	O	O	–	O	×	×
5		×	O	–	O	×	×
6		O	×	–	O	×	×
7		O	×	O	×	×	×
8	"Bridging study"	O	O	–	O	×	×
9		×	O	–	O	–	–
10		O	×	–	O	–	–
11		×	×	–	O	O	×
12	"Global clinical trial"	O	O	–	×	–	O
13		O	×	–	–	–	O
14		O	×	–	O	O	×
15		×	×	–	O	–	O
16		×	×	–	×	–	O
17		×	×	O	×	O	×
18	"Foreign trial"	×	×	–	O	×	×
19		×	×	O	×	×	×
20	"No efficacy/safety trial"	×	×	×	×	×	×

CDS, clinical development strategy; NDA, new drug application; PMDA, Pharmaceuticals and Medical Devices Agency.

A "Key clinical trial" was defined as an important clinical trial for efficacy evaluation in making an approval decision among "major sources for evaluation," as described in the PMDA review reports. The "Key clinical trial" was also classified into exploratory trial and confirmatory trial categories. The confirmatory trial was defined as a phase III trial that had a control arm with randomization, and the other trials, such as single-arm studies, were classified as exploratory trials. A trial that was designed as confirmatory, had larger sample size, or included Japanese patients was given higher priority for the classification of CDSs.

O: A clinical trial defined as a "Key clinical trial" was included in the clinical data package.

×: No clinical trial was included as the "major source for evaluation" in the review report.

–: Clinical trial data were either included or not included in the clinical data package of an NDA.

of a single molecular entity were included in a report, we considered them as $n = 1$ for the analysis. If multiple dates were included in the report as the NDA submissions dates for two or more formulations for a single molecular entity, the earliest submission date was used for the analysis.

LDD analysis. LDD was determined from the time difference in drug development and was calculated by subtracting the NDA submission date of a drug to the FDA (United States) from its submission date to the PMDA (Japan). Thus, if the NDA submission date of a drug was earlier in Japan, the difference took a negative value. If a drug was not approved in the United States, the difference was estimated as zero.

Classification of CDS. To determine the relationship between CDSs and LDD, CDSs were characterized based on the type of (Key clinical trial). A "Key clinical trial" was defined as an important clinical trial for efficacy evaluation in making an approval decision among "major sources for evaluation" ("HYOUKA SIRYO" in Japanese), as described in the PMDA review reports. If a clinical trial was mentioned as a "reference" (SANKO SIRYO" in Japanese) in a review report, the trial was not classified as a (Key clinical trial). If an indication included in a review report was for both adults and children, clinical trials for the children were excluded from the analysis. The "Key clinical trial" was also classified into exploratory trial or confirmatory trial categories. A confirmatory trial was defined as a phase III trial that had a control arm with randomization, and other trials, such as a single-arm study, were classified as exploratory trials. A trial that was designed as confirmatory, had a larger sample size, or included Japanese patients was given higher priority for the classification of CDSs. CDSs for the above-described classification were collected independently by three authors (T.U., Y.A., and A.T.), and the differences were reconciled by consensus.

On the basis of the conditions described above, we identified 20 styles of strategies (summarized in **Table 2**). These 20 styles were generalized into six CDSs, namely, "Local trial," "Local and foreign trials," "Bridging study," "Global clinical trial," "Foreign trial," and "No efficacy/safety trial." Three review reports (insulin glulisine, fesoterodine fumarate, and tofacitinib citrate) included both bridging study and GCT, but they were categorized into "Bridging study" because the pivotal data involving the Japanese population for the NDA review came mainly from the bridging study. Each drug was categorized into one of six CDSs and was not categorized under more than one CDS.

Percentage of Japanese subjects included in the data package. For calculating the percentage of the total number of subjects in an NDA who were Japanese subjects, the numbers of Japanese living in Japan and total subjects involved in the efficacy/safety trials included in the clinical data package of an NDA were collected from the review reports and common technical documents. The number of patients who actually took a drug was generally counted, but if such data were unavailable (as in five cases), the number of enrolled subjects was used for the calculation. The data described above were not available for two drugs, and these were excluded from the analysis.

Data analysis. For the analysis of time difference in drug development period and percentage of Japanese subjects among total subjects, the median and several percentile values (10th, 25th, 75th, and 90th percentiles) were calculated. The Wilcoxon signed-rank test and Wilcoxon rank-sum test were used for examining the statistical significance; $P < 0.05$ was considered to be statistically significant. TIBCO Spotfire S+ 8.1J software (TIBCO Spotfire, Somerville, MA) was used for the data analysis.

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/cpt

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AUTHOR CONTRIBUTIONS

T.U., Y.A., and Y.U. wrote the manuscript. Y.U. designed the research. T.U., Y.A., A.T., H.Y., and M.N. performed the research. T.U., Y.A., and A.T. analyzed the data.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

✓ Japan has struggled for many years with the so-called "drug lag," a lag in drug approval as compared with that in the United States and the European Union. Through several measures taken by the government, the lag in the regulatory review, but not the LDD, has dramatically decreased. Thus, the current issue that remains to be resolved is how to decrease the LDD in Japan.

WHAT QUESTION DID THIS STUDY ADDRESS?

✓ This analysis addressed the effects of various clinical development strategies on the LDD.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ The analysis clearly identified several factors affecting the LDD. One factor that significantly decreased LDD is the inclusion of GCTs in the clinical development strategy. Another key factor that minimized LDD was considering a development strategy as early as possible.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

✓ These results provide new insights into consideration of a clinical development strategy for drugs submitted for regulatory approval in Japan.

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The risk of cutaneous adverse reactions among patients with the *HLA-A* 31:01* allele who are given carbamazepine, oxcarbazepine or eslicarbazepine: a perspective review

Nahoko Kaniwa and Yoshiro Saito

Abstract: Carbamazepine is a drug that is widely used for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder. This drug is also known to cause cutaneous adverse drug reactions (cADRs) in up to 10% of patients. The recent progress in pharmacogenetics has revealed that human leukocyte antigen (HLA) genotypes are associated with a susceptibility to the cADRs caused by particular drugs. For carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis, very strong associations with *HLA-B*15:02* have been found mainly in patients of Southeastern Asian origin. In some countries, prescreening *HLA-B*15:02* allele has already been put to practical use as a biomarker to avoid the life-threatening adverse drug reactions. In this review, another risk factor for carbamazepine-induced cADRs is discussed, namely *HLA-A*31:01*. We compare the strength of the association between *HLA-A*31:01* and carbamazepine-induced cADRs based on reports for various ethnic populations; discuss the difference between the *HLA-A*31:01* and *HLA-B*15:02* biomarkers and the usefulness of prescreening *HLA-A*31:01* to detect patients at high risk for carbamazepine-induced cADRs; and refer to points that remain to be resolved.

Keywords: Biomarker, HLA genotype, hypersensitivity syndrome, Stevens–Johnson syndrome, toxic epidermal necrolysis

Introduction

Carbamazepine is one of most commonly prescribed drugs for the treatment of epilepsy, trigeminal neuralgia and bipolar disorder. It is also known to be the most common inducer of cutaneous adverse drug reactions (cADRs). The clinical manifestations of cADRs caused by carbamazepine vary widely, ranging from a mild skin rash, such as maculopapular eruption (MPE) and erythema exsudativum multiforme (EEM) minor, to severe rashes such as EEM major, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug-induced hypersensitivity syndrome (DIHS). SJS and TEN, with their characteristic mucosal and cutaneous disorders, including blisters, are considered to represent different severities of the same disease [Bastuji-Garin *et al.* 1993]. The most widely accepted classification for these two disorders is based on the degree of skin detachment expressed in terms of the percentage of body surface area affected. SJS is defined as an area of skin detachment that involves less than 10% of the body surface. SJS–TEN overlap is defined as an area of skin detachment that affects from 10% to less than 30% of the body surface. TEN is defined as a level of skin detachment of no less than 30%. DIHS and MPE are categorized as nonbullous cADRs [Naisbitt *et al.* 2003]. DIHS is a severe adverse reaction that leads to multiorgan failure and is hypothesized to be associated with the reactivation of herpesvirus 6 [Hashimoto, 2006]. DIHS has also been referred to as a drug reaction with eosinophilia and systemic symptoms (DRESS)

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or hypersensitivity syndrome (HSS). In this review, either DIHS or HSS is used according to the disease name used in the original article. Whereas MPE is a mild skin rash, SJS/TEN and DIHS are life-threatening adverse reactions. The incidences of SJS/TEN and DIHS are very low (two to three cases per million per year), but their mortality is very high (5–30%). SJS/TEN is currently understood to be reactions that involve cytotoxic CD8+ T cells, and DIHS and MPE are also believed to have immune etiologies [Naisbitt *et al.* 2003].

The occurrence of cADRs is a very significant problem, both for physicians and patients, because it is unpredictable and often leads to a discontinuation of treatment. However, recent studies have revealed that human leukocyte antigen (HLA) genotypes are linked to a predisposition to the cADRs induced by particular drugs, including carbamazepine, and these genotypes are thus thought to be promising biomarkers. In this review, the associations between *HLA-A*31:01* and cADRs induced by carbamazepine and its analogs are discussed.

HLA proteins

HLAs are a family of proteins that are involved in immune reactions by presenting antigens to T cells. HLA-A, -B and -C are categorized as class I molecules that are ubiquitously expressed on the surface of cells, including keratinocytes. HLA-DR, -DQ, and -DP are categorized as class II molecules that are expressed mainly on the surface of antigen-presenting cells, such as B cells, macrophages and dendritic cells. The genes for all the HLAs are on the short arm of chromosome 6 and are known to be highly polymorphic. For example, more than 1000 alleles of *HLA-A, -B* and *-C* have been identified to date [Robinson *et al.* 2011].

A brief introduction of associations of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis with HLA-B*15:02 and HLA-B75

Very strong associations between *HLA-B*15:02* and carbamazepine-induced SJS/TEN have been found among the Han Chinese in Taiwan [Hung *et al.* 2006; Chung *et al.* 2004], which were confirmed by various case–control studies of Southeastern Asian patients [Kulkantrakorn *et al.* 2011; Wang *et al.* 2011; Zhang *et al.* 2011; Tassaneeyakul *et al.* 2010; Mehta *et al.* 2009; Locharernkul *et al.* 2008; Man *et al.* 2007; Lonjou *et al.* 2006]. *HLA-B*15:02* is a member of the serotype HLA-B75. In addition to *HLA-B*15:02*, carriers of some HLA-B75 members, including *HLA-B*15:08, HLA-B15:11* and *HLA-B*15:21*, with carbamazepine-induced SJS/TEN have also been detected in Asian countries, including India, Thailand, Korea and Japan [Kaniwa *et al.* 2010; Tassaneeyakul *et al.* 2010; Mehta *et al.* 2009]. The involvement of HLA-B75 members in the development of SJS/TEN was suggested by an *in vitro* study using a cell line transfected with cDNAs of these alleles, which underwent lysis by cytotoxic T cells activated by carbamazepine through recognition by the T-cell receptor (TCR) [Wei *et al.* 2012]. Thus, HLA-B75 can be said to be a risk factor for carbamazepine-induced SJS/TEN in Asian individuals. It is noteworthy that *HLA-B*15:02* is a risk factor only for SJS/TEN but not for other phenotypes of cADRs, and is also restricted to patients of Asian origin.

Associations of carbamazepine-induced cADRs with HLA-A*31:01

As shown in Table 1, *HLA-A*31:01* was reported for the first time to have associations with carbamazepine-induced MPE/HSS, but not with SJS/TEN, in Han Chinese patients in Taiwan [p = 0.0022, odds ratio (OR) = 17.5, 95% confidence interval (CI) = 4.6–66.5] [Hung *et al.* 2006]. The sensitivity of *HLA-A*31:01* in Han Chinese patients with carbamazepine-induced MPE/HSS was 0.25. This was followed by a report by Kashiwagi and colleagues that allelic frequency of *HLA-A*31:01* in Japanese patients with carbamazepine-induced severe cADRs (n = 22 including four SJS cases) was significantly higher than in a general Japanese population (p = 0.0004, OR = 4.33 and sensitivity = 0.50) [Kashiwagi *et al.* 2008]. The following five studies listed in Table 1, including our unpublished data, also revealed the tendency of a high allelic or carrier frequency of *HLA-A*31:01* in both SJS/TEN and various other types of cADRs, including DIHS/HSS, EEM or MPE, compared with that in tolerant control patients or in general populations. It should be noted, however, that the p values are dependent on the sample sizes of the studies, and sometimes no significant differences were detected because of a small sample size. In a study with Korean patients, three of seven patients with SJS/TEN and 10 of 17 patients with HSS carried *HLA-A*31:01*, and the carrier frequency in the latter was significantly higher than in tolerant

Table 1. Association of *HLA-A*31:01* or A31 with carbamazepine-induced cutaneous adverse reactions.

cADR phenotypes	Ethnic groups	Carrier frequency		*p* value	Odds ratio	95% Confidence interval	Reference
		Case group	Tolerant control group				
SJS/TEN	Han Chinese in Taiwan	1/60	4/144	NS			Hung *et al.* [2006]
MPE/HSS		8/31	4/144	0.0021	12.17	3.6–41.2	
HSS		2/13	4/144	NS			
MPE		6/18	4/144	2.2E-03	17.5	4.6–66.5	
Severe cADRs*	Japanese	11/22	53/371§	0.0004‡	4.33	2.07–9.06	Kashiwagi *et al.* [2008]
All phenotypes	Japanese	45/77	54/420	1.1E-19	9.5	5.6–16.3	Ozeki *et al.* [2011]
DIHS		21/36	54/420	2.1E-09	9.5	4.6–19.5	
SJS/TEN		5/6	54/420	2.4E-04	33.9	3.9–295.6	
Others		19/35	54/420	4.7E-08	8	3.9–16.6	
All phenotypes	Japanese	10/15	5/33	< 0.001	11.2	2.668–47.105	Niihara *et al.* [2012]
SJS/TEN		1/3	5/33				
DIHS		8/9	5/33				
EEM/MPE		1/3	5/33				
SJS/TEN	Japanese	9/21	484/2878§	0.0047	3.7	1.55–8.86	Our data (unpublished)
SJS	Korean	3/7	7/50	NS			Kim *et al.* [2011]
HSS		10/17	7/50	0.001 (p_c = 0.013)	7.3	2.3–22.5	
SJS	European	5/12	10/257	8.0E-05	25.93	4.93–116.18	McCormack *et al.* [2011]
HSS		10/27	10/257	3.5E-08	12.41	1.27–121.03	
MPE		23/106	10/257	1.1E-06	8.33	3.59–19.36	
SJS	Children originating from various ethnicities and living in Canada	0/9	3/91	NS			Amstutz *et al.* [2013]
HSS		3/6	3/91	0.0025	26.36	2.53–307.89	
MPE		6/26	3/91	0.0037	8.57	1.67–57.50	

*Erythroderma maculopapular and nutiform, $n = 6$; erythroderma, $n = 3$; DIHS, $n = 4$; SJS, $n = 2$ and other drug eruptions, $n = 7$.
§General population
‡Allelic frequencies were compared.
cADR, cutaneous adverse drug reaction; DIHS, drug-induced hypersensitivity syndrome; EEM, erythema exsudativum multiforme; HSS, hypersensitivity syndrome; MPE, maculopapular eruption; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

controls or a general population [Kim *et al.* 2011]. The sensitivity of *HLA-A*31:01* in Korean patients with carbamazepine-induced SJS or HSS was 0.54 (13/24). In a study of Japanese patients conducted by Ozeki and colleagues, *HLA-A*31:01* was significantly associated with carbamazepine-induced DIHS, SJS/TEN and other types of skin rashes (sensitivity for all phenotypes = 0.58) [Ozeki *et al.* 2011]. In their study, an especially strong association was detected between SJS/TEN and *HLA-B*31:01*. In another Japanese study by Niihara and colleagues, eight of nine patients with carbamazepine-induced DIHS carried *HLA-A*31:01*, an association that was statistically significant (sensitivity for all phenotypes = 0.67) [Niihara *et al.* 2012]. We previously reported the involvement of *HLA-B*15:11* in the development of carbamazepine-induced SJS/TEN in Japanese patients [Kaniwa *et al.* 2010]. In our sample, 9 of 21 patients with carbamazepine-induced SJS/TEN carried *HLA-A*31:01*, and the association was statistically significant ($p = 0.0047$, OR = 3.7, 95% CI = 1.55–8.86; sensitivity = 0.43) (unpublished data). *HLA-A*31:01* was also reported to be a biomarker for various carbamazepine-induced cADRs in Europeans, ranging from a mild skin rash, such as MPE, to severe cADRs, including SJS/TEN, and the sensitivity of *HLA-A*31:01* for all phenotypes was 0.26 (38/145) [McCormack *et al.* 2011]. The situation that *HLA-A*31:01* is involved in various phenotypes of skin rash caused by carbamazepine in white patients was similar to those observed in Asian patients. A recently conducted case–control study including children living in Canada also detected significant correlations of *HLA-A*31:01* with carbamazepine-induced HSS and MPE, but there were no correlations with SJS [Amstutz *et al.* 2013]. In this study, three patients with SJS who were of Asian origin carried the *HLA-B*15:02* allele.

As mentioned above, the sensitivities of *HLA-A*31:01* observed in studies with Korean and Japanese patients ranged from 43% to 67%, and they were higher than those observed among Han Chinese in Taiwan and among Europeans (26% for both ethnic groups). However, the observed variation in association strengths of *HLA-A*31:01* with carbamazepine-induced cADRs among various ethnic groups was smaller than that in associations of *HLA-B*15:02* with carbamazepine-induced SJS/TEN. Yip and colleagues estimated a pooled OR of 9.5 (95% CI = 6.4–13.9) for the association of *HLA-A*31:01* with carbamazepine-induced cADRs among the studies with Korean, Japanese, Chinese and European patients [Yip *et al.* 2012].

Population allelic frequency of HLA-A*31:01 in various ethnic groups

The *HLA-A*31:01* allele in general populations varies among different ethnic groups [Kurose *et al.* 2012]. *HLA-A*31:01* is a common allele among Japanese individuals (allelic frequency 0.071–0.093). Its frequency is comparable among Korean individuals and white individuals (0.050, and 0.018–0.042 respectively) and is lower among Chinese in both mainland China and Taiwan (0.022 and 0.018 respectively). HLA-A*31:01 is a rare allele among African individuals, in whom its frequency is on average 0.01. There have been no reports on whether *HLA-A*31:01* is linked to carbamazepine-induced cADRs in African patients.

Comparison between HLA-B*15:02 and HLA-A*31:01 as risk factors for carbamazepine-induced cutaneous adverse drug reactions

Although, as mentioned above, the association between *HLA-B*15:02*/HLA-B75 and carbamazepine-induced SJS/TEN appears to be restricted to Asian patients, associations between *HLA-A*31:01* and carbamazepine-induced cADRs have been detected both in Asian and European patients. However, its associations with cADRs were rather weak compared with the associations between *HLA-B*15:02* and carbamazepine-induced SJS/TEN observed in Southeast Asian countries, for which the sensitivities were nearly 100%.

At first, the association of *HLA-A*31:01* was thought to be limited to carbamazepine-induced HSS or MPE, but not with SJS/TEN in Han Chinese populations. However, various case–control studies that were conducted independently in other Asian countries and in Europe showed significant correlations between *HLA-A*31:01* and the SJS/TEN caused by carbamazepine. Therefore, it can be concluded that *HLA-A*31:01* is involved in the onset of both SJS/TEN and nonbullous cADRs, such as HSS and MPE.

The mechanism by which small molecules such as drugs (<1000 Da) become antigenic and recognized by T cells has not been elucidated. Two major concepts have been proposed [Adam *et al.* 2011]. One is the hapten/prohapten concept, and

the other is the p-i concept (pharmacological interactions of drugs with immune receptors). β-Lactam antibiotics have been shown to bind covalently to lysine residues of serum albumin as a hapten, and peptides modified with a hapten, which are generated by intracellular processing, embedded in HLA molecules are considered to be presented by antigen-presenting cells to TCRs (hapten concept) [Monshi *et al.* 2013; Jenkins *et al.* 2009]. Using a cell line transfected with *HLA-B*15*, Wei and colleagues showed that HLA-B75 members, including *HLA-B*15:02* and *HLA-B*15:11* proteins, promoted cell lysis by cytotoxic T cells that had been activated by carbamazepine [Wei *et al.* 2012]. In contrast, members of other serotypes of *HLA-B*15*, such as HLA-B62 and HLA-B72, cannot promote cell lysis by cytotoxic T cells activated by carbamazepine. The 63rd amino acid (the next amino acid of putative carbamazepine binding site) of members of serotype HLA-B75 is asparagine, whereas that of serotypes HLA-B62 or HLA-B72 is glutamic acid. Thus, carbamazepine is bound noncovalently to the HLA-B75 molecules, and the TCR recognizes its complex for T-cell activation (p-i concept). In addition to the specific HLA allele, *HLA-B*15:02*, a skewed usage of specific repertoires of the third complementarity-determining region of the TCR, such as VB-11-ISGSY, is reported to be required to develop carbamazepine-induced SJS/TEN [Ko *et al.* 2011].

To date, no information has been available on the pathogenic mechanisms of *HLA-A*31:01* molecules inducing hypersensitive reactions to carbamazepine (or its metabolites), including mechanisms of antigen presentation and TCR recognition. The pathogenesis for the HLA-A*31:01 molecule may be different from that for HLA-B*15:02 molecules, because *HLA-A*31:01* is linked not only to SJS/TEN but also to various phenotypes of cADRs. The diverging points for such clinical manifestations should be clarified.

The alleles *HLA-A*31:01* and *HLA-B*15:11* were found exclusively in each case of our Japanese patients (our unpublished data) and of Korean patients [Kim *et al.* 2011]. Unlike other ethnic groups, either *HLA-A*31:01* or *HLA-B*15:11* can be said to be a risk factor for carbamazepine-induced SJS/TEN in Korean and Japanese individuals because more than half of the patients with carbamazepine-induced SJS/TEN in these countries carry either of the alleles (6/7 in Korean patients and 14/21 in Japanese patients) [Kim *et al.* 2011] (our unpublished data). Therefore, the combined biomarkers may be of use to detect patients at high risk of carbamazepine-induced SJS/TEN in Korean and Japanese individuals.

Cutaneous adverse drug reactions caused by oxcarbazepine and eslicarbazepine

Oxcarbazepine and eslicarbazepine, which are metabolized differently from carbamazepine, have been developed to avoid the severe adverse reactions caused by carbamazepine. Oxcarbazepine was approved in 2007 in the USA and eslicarbazepine was approved in 2009 in Europe. Although SJS/TEN cases caused by oxcarbazepine were fewer than those caused by carbamazepine [Buggy *et al.* 2010; Dogan *et al.* 2008; Le Louët *et al.* 2008], there have been many reports of oxcarbazepine-caused severe cADRs. To date, two studies with Chinese patients have pointed out the involvement of *HLA-B*15:02* in oxcarbazepine-induced SJS/TEN [Hu *et al.* 2011; Hung *et al.* 2010]; however, another study with Chinese patients detected no significant correlation between the disease and this allele [He *et al.* 2012]. There have been no reports concerning the involvement of *HLA-A*31:01* in oxcarbazepine-induced SJS/TEN. Since eslicarbazepine, which is the active metabolite of oxcarbazepine, was approved only quite recently, reports on severe cADRs have not been accumulating.

Usefulness of prescreening HLA-A*31:01

On the basis of the knowledge obtained from various retrospective case–control studies with Southeastern patients [Kulkantrakorn *et al.* 2011; Wang *et al.* 2011; Zhang *et al.* 2011; Tassaneeyakul *et al.* 2010; Mehta *et al.* 2009; Locharernkul *et al.* 2008; Man *et al.* 2007; Hung *et al.* 2006; Lonjou *et al.* 2006; Chung *et al.* 2004] and a positive result obtained from a prospective case–control study performed in Taiwan to examine the usefulness of prescreening the risk factor [Chen *et al.* 2011], the screening for *HLA-B*15:02* prior to the initiation of carbamazepine treatment is currently mandatory in Taiwan and Singapore, and for patients in the USA who have ancestry at high risk for carbamazepine-induced SJS/TEN.

For *HLA-A*31:01*, Yip and colleagues [Yip *et al.* 2012] examined the usefulness of prescreening by a meta-analysis, using data obtained from three studies [McCormack *et al.* 2011; Ozeki *et al.*

2011; Hung *et al.* 2006]. The performance characteristics of *HLA-A*31:01* for Han Chinese, Japanese and European patients estimated by Yip and colleagues are as follows: sensitivity 0.262–0.584; specificity 0.871–0.972; positive predictive value 0.119–0.427; and negative predictive value 0.921–0.986. In every ethnic group, the number of patients needing to be tested in order to prevent one case (NNT) was estimated at less than 100, which was much smaller than the NNT (461) for screening *HLA-B*15:02* for Taiwanese individuals [Yip *et al.* 2012]. This difference may be caused by the fact that *HLA-B*15:02* is linked only with the rarer, but more severe cADRs, SJS/TEN, whereas *HLA-A*31:01* is linked even with frequently occurring mild skin rashes, such as MPE, as well as with SJS/TEN. The usefulness of *HLA-A*31:01* prescreening should be further discussed taking several points into consideration: the clinical impact of avoiding mild skin reactions, alternative drugs for *HLA-A*31:01*-positive patients and cost-effectiveness of the prescreening test. The results of an ongoing prospective study on the effects of a *HLA-A*31:01* prescreening test for prevention of carbamazepine-induced cADRs conducted in Japan by a Riken group (M. Kubo, http://www.biobankjp.org/pgx/outline/cbz.html) would have much impact on this issue.

Because HLA genotyping methods currently being used in clinical laboratory testing are laborious, time consuming and expensive, a more inexpensive, simple and rapid genotyping method is required for prescreening *HLA-A*31:01*. A new, simple and rapid pharmacogenetic test for detecting *HLA-A*31:01* was developed, which uses the InvaderPlus (Hologic, Inc., Bedford, MA, USA) assay and surrogate single-nucleotide polymorphisms that were found by a genome-wide association study to be highly linked with *HLA-A*31:01* [Aoki *et al.* 2012]. Uchiyama and colleagues developed another simple and inexpensive method for the detection of *HLA-A*31:01*, using a nested *HLA-A* allele-specific primer polymerase chain reaction combined with restriction fragment length polymorphism analysis [Uchiyama *et al.* 2013].

Conclusion

Unlike the case of HLA-B**15:02*, *HLA-A*31:01* is a risk factor for various types of carbamazepine-induced cADRs, ranging from mild ones such as MPE to severe ones, including SJS/TEN and DIHS, in both Asian and white patients. The pathogenesis of *HLA-A*31:01* involvement in the development of cADRs remains to be elucidated, which could help discriminate rashes that are likely to progress from those that are likely to resolve.

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Conflict of interest statement

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors have any conflict of interest to disclose.

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