

*This English version of the record of the consultation has been published by PMDA. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.*

(Attachment 1)

## Record of the Consultation on Pharmacogenomics/Biomarkers

November 2, 2018

Pharmaceuticals and Medical Devices Agency

Concerning the following consultation on Pharmacogenomics/Biomarkers requested, the background of the consultation submitted by applicant (hereinafter referred to as the “applicant”) and the summary of an evaluation by the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as the “PMDA”) are as described herein.

It should be noted that decisions in this document were made on the scientific level at the time of face-to-face consultation based on the data submitted by the applicant. Interpretation for the validity of the decisions may vary based on possible new findings and scientific advances, etc.

Date/No. of reception:	March 28, 2018/No. P-BM4
Biomarkers consulted:	Urinary clusterin, urinary cystatin C, urinary kidney injury molecule-1 (KIM-1), urinary <i>N</i> -Acetyl- <i>beta</i> - <i>D</i> -Glucosaminidase (NAG), urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary osteopontin, urinary total protein, and urinary albumin
Consultation category:	Additional consultation on pharmacogenomics/biomarkers (key points of clinical trial protocols)
Consultation applicant:	Critical Path Institute’s Predictive Safety Testing Consortium (PSTC)
Department in charge (Section):	Omics Working Group

## 1. Background

The applicant is working to obtain the qualification of novel nephrotoxicity biomarkers (hereinafter, "Novel BMs"). The early stage clinical application of Novel BMs (Learning Phase and Confirmatory Phase) was last discussed with PMDA at the Pharmacogenomics/Biomarker Consultation (hereinafter, "Previous Consultation"). At this consultation the applicant discussed the plan for qualification of 8 Novel BMs (urinary clusterin, urinary cystatin C, urinary kidney injury molecule-1, urinary *N*-Acetyl-*beta*-*D*-glucosaminidase, urinary neutrophil gelatinase-associated lipocalin, urinary osteopontin, urinary total protein, and urinary albumin) which are considered to be applicable for prediction of renal injury in medical practice based on the results of clinical studies in the Learning Phase. The applicant requested the current consultation to provide an update since the previous consultation, and to confirm the PMDA's opinion on the following 3 consultation items related to the bridging study in Japanese subjects.

## 2. Consultation items and opinion of the PMDA

Consultation Item 1: Appropriateness to use the results of Confirmatory Phase clinical studies in non-Japanese subjects (Cisplatin Study and Aminoglycoside Study) and a Learning Phase clinical study [PSTC-initiated study in healthy subjects (hereinafter, "HV Study") and a clinical study in mesothelioma patients (hereinafter, "MM Study")] as base data for the bridging study of Novel BMs in Japanese subjects

### (1) Opinions of the PMDA

PSTC's strategy is acceptable, which is to extrapolate the results of the study of Novel BMs conducted previously in non-Japanese to Japanese subjects upon comparison with the results obtained from studies of Novel BMs to be conducted in Japanese subjects in the future ([1] Clinical study in Japanese healthy subjects, and [2] Clinical study in Japanese patients exposed to a nephrotoxic drug; hereinafter, "Bridging Study").

Also, PMDA has no particular objection to using the results of clinical studies conducted in non-Japanese (Cisplatin Study and Aminoglycoside Study, which are currently ongoing, and HV Study and MM Study, which have been completed) as non-Japanese data for comparison with Japanese study data; provided that the currently-ongoing Cisplatin Study and Aminoglycoside Study will be completed appropriately and generate the expected results.

Meanwhile, at least, the following points should be noted as potential issues associated

with comparison between Japanese and non-Japanese study data.

- The applicant needs to provide an appropriate explanation to justify the following points based on the results of the Cisplatin Study and Aminoglycoside Study to be obtained in the future:
  - Appropriateness of the threshold set out based on the results of HV Study and MM Study ( $T_{SS}$  assumed to be within a normal range, and  $T_{MS}$  assumed to be a medically-significant threshold),
  - Significance to set out 2 thresholds ( $T_{SS}$  and  $T_{MS}$ ),
  - The assessment criteria using these thresholds (Guiding Principles),
  - The applicant's claim that renal injury in any region would be detectable by combining Novel BMs.
- The materials presented by the applicant do not adequately explain the possibility of a factor other than nephrotoxic drugs (concomitant drug, surgical invasion, and blood transfusion, etc.) affecting the evaluation of Novel BMs in the MM Study. Therefore, the applicant needs to present the details of the subjects' background in the Cisplatin Study and Aminoglycoside Study (especially by subgroups stratified by the presence/absence of nephrotoxic drug use) and demonstrate how the response of Novel BMs to kidney injury attributable to the nephrotoxic drug can be appropriately evaluated.

## (2) Responses of applicant to the PMDA's opinions

Applicant has acknowledged the opinions of the PMDA. Of the points suggested by the PMDA as topics when comparing the results from Japanese and non-Japanese subjects, applicant will complement each of the following items as described below: 1) the use of the Novel BMs in combination and 2) the possibility of factors other than renal toxic drugs affecting assessment of the Novel BMs:

- 1) In nonclinical studies, the response of Novel BM has been evaluated using histopathological findings as basic renal toxicity parameters. The combination of the Novel BMs, which are likely to be associated with impairment in various specific sites of the kidneys, is expected to improve detection sensitivity for renal toxicity. However, based on evidence obtained so far, the applicant finds that the Novel BMs cannot be concluded to be suitable for predicting impairment in specific sites of the nephron when used in clinical studies.

2) The Novel BMs are assumed to show responses to not only drug-induced renal injury but also renal injury caused by other factors (e.g., concomitant medications, surgical invasion, and blood transfusion). Thus, the applicant will carefully examine in detail the background characteristics of the subjects of the clinical studies (cisplatin study and aminoglycoside study) in the confirmatory phase and then properly evaluate the Novel BM response to drug-induced renal injury. The applicant expects to be able to present the results of this examination during the second quarter of 2019.

(3) Discussion at the consultation meeting and what need to be discussed in future.

The PMDA stated:

The explanations provided in the above Items 1) and 2) may be generally acceptable. The PMDA, however, thinks that it is important to make the background characteristics of subjects in renal toxic drug treatment and non-renal toxic drug treatment groups in the bridging studies in Japanese subjects as similar as possible to those in the clinical studies (cisplatin study and aminoglycoside study) in the confirmatory phase so that ethnic differences in the Novel BMs for drug-induced renal disorder can be properly assessed.

The applicant understood the opinions of the PMDA.

In addition, the PMDA commented as follows: As the PMDA pointed out at the Previous Consultation, changes over time in the Novel BMs (e.g., timing when the biomarkers start to elevate, the duration and recovery of the evaluation, etc.) are considered to be important information for correctly understanding the nature of the Novel BMs and measuring them in a timely manner; thus, such changes should be evaluated to the extent possible based on the results of the studies in the confirmatory phase and the bridging studies in Japanese subjects.

The applicant stated that they intend to continue examining changes over time in the Novel BMs while taking into account that data obtained so far showed that Novel BM responses tend to vary depending on renal toxic drugs.

Consultation Item 2: Appropriateness to determine that the analytical method using the 8 Novel BMs have been validated based on the concept of "fit-for-purpose" for uses in the Bridging Studies to be conducted in Japanese subjects

(1) Opinions of the PMDA

PMDA has no particular objection to use of the analytical methods for the 8 Novel BMs used in non-Japanese clinical studies in the Bridging Study. Also, it is acceptable to use the same laboratory that was used in clinical studies conducted in non-Japanese subjects (Pacific Biomarkers, Inc.; hereinafter, "PBI"), or other laboratories which are validated to be of an equivalent quality as PBI for measurement of Novel BMs other than urinary albumin.

Meanwhile, at least, the following points should be noted as potential issues associated with the analytical method for the 8 Novel BMs.

- Urinary clusterin does not demonstrate long-term stability, and therefore, a duration validated for stability should be identified before the start of the Bridging Study and the measurement should be performed within that duration.
- In order to use Novel BMs broadly, the applicant should verify that they are also measurable in laboratories other than PBI before the qualification.
- It is acceptable to invalidate urine samples with blood contamination that may interfere with the analysis. Meanwhile, the applicant should consider an additional analysis without exclusion of such samples in case there are too many samples invalidated due to blood contamination.

(2) Responses of applicant to the PMDA's opinions

The applicant has acknowledged the opinions of the PMDA. The applicant provides updates on 1) the status at facilities other than PBI with the ability to run the Novel BM assays and 2) the handling of urine samples with blood contamination.

- 1) At present, assay validation by a PSTC member company is ongoing, and the analytical methods for the Novel BMs are expected to become available at facilities other than PBI.
- 2) It is not planned to additionally analyze urine samples invalidated due to blood contamination because only two of the approximately 1,300 urine samples were excluded due to blood contamination in clinical studies conducted so far, and it has

been revealed that blood contaminating samples interferes with the detection of some of the novel BMs (e.g., KIM-1). If data are missing for the analysis of the Novel BMs in the clinical studies due to blood contamination in the confirmatory phase, analysis of samples collected at a time point immediately after that at which the data are missing will be substituted.

(3) Discussion at the consultation meeting and what need to be discussed in future.

The PMDA has asked the applicant when the validation by PSTC member company will be completed.

Applicant has responded that the validation by said company will be completed before the initiation of the clinical study involving Japanese patients who were exposed to renal toxic drugs. Therefore, validation results can be presented during an additional consultation with the PMDA in the future to facilitate discussion around the plan for the clinical study involving Japanese patients.

The PMDA has commented as follows:

With regard to the explanation in the above Item 2), considering that the number of invalid samples due to blood contamination was extremely limited in the previously completed clinical studies, the PMDA finds that there is no notable concern regarding the applicant's policy. If analysis results of invalid samples are imputed using those of other samples, when holding an additional consultation on the plan for the bridging studies, applicant is required to explain its appropriateness with presentation of the details of the imputation method.

Applicant has accepted the PMDA's suggestion.

Consultation Item 3: Acceptability of the bridging strategy intended to evaluate the ethnic differences based on the results of the 4 clinical studies conducted in non-Japanese subjects (Cisplatin Study, Aminoglycoside Study, HV Study and MM Study) compared on a step-by-step basis, first with data in Japanese healthy subjects, and then with the data in Japanese subjects with renal impairment so as to verify the qualification of the 8 Novel BMs in Japanese subjects.

(1) Opinions of the PMDA

The applicant's step-by-step approach to evaluate the ethnic differences in Novel BMs is acceptable; provided that at least 1) and 2) below are considered for the Bridging Study to be conducted in the future for the qualification of the 8 Novel BMs in the Japanese population.

1) Clinical study in Japanese healthy subjects

Respond to the following points. Meanwhile, it is acceptable to change the sample collection timepoints to 5 ( $\pm 1$ ) days from the study start, like in the HV Study.

- This study should be conducted as a prospective study in order to appropriately compare the data collected with the results of the HV Study, which was also conducted as a prospective study.
- If a success criteria is not defined in advance in this study which is intended to obtain basic data on Novel BMs (such as normal range, etc.) in the Japanese population, the study results including those of clinical studies to be conducted in Japanese patients may become difficult to interpret. Therefore, the applicant should set out a criteria to demonstrate "similarities" or "the absence of problematic difference" compared to the results of HV Study (for instance, the confidence interval of the specificity in this study to be within X% of the confidence interval of the specificity in HV Study), in addition to visual inspection and/or other descriptive statistical assessments as a statistical analysis technique.
- The appropriateness of 40 subjects as a sample size should be reconsidered in addition to the PMDA's opinion on this study presented above.

2) Clinical study in Japanese patients exposed to nephrotoxic drugs

The details of this study design (e.g., criteria to determine the similarities between Japanese and non-Japanese as later described, as well as Novel BMs subject to evaluation, etc.) should be discussed again based on the HV study results mentioned in above Item

1). The applicant should consider the following points for concrete discussion on the study design.

- In order to enable accurate discussions on the similarities in Novel BMs between Japanese and non-Japanese, this study should be conducted as a prospective study, and all factors except for the ethnic (regional) factors (e.g., underlying disease, the severity of renal function, types of nephrotoxic drugs, and timepoints for sample collection, etc.) should be the same, as much as possible, as those of prospective studies conducted in non-Japanese subjects.
- Comparisons based on the data such as sensitivity, specificity, and ROC (Receiver Operating Characteristic) analysis are important in evaluating the similarities of Novel BMs between Japanese and non-Japanese; thus, subjects not receiving a nephrotoxic drug should be also enrolled in the study so as to discuss these data in Japanese patients. Moreover, as shown in the PMDA's opinion in above 1), carefully consider the necessity to set out criteria that enables appropriate judgment of the similarities.
- The appropriateness of 40 subjects as a sample size should be re-discussed along with the above opinion of PMDA.

(2) Responses of applicant to the PMDA's opinions

1) Clinical study in healthy Japanese subjects

The applicant has acknowledged the opinions of the PMDA and will conduct the study set forth in the above Item 1) as a prospective study.

As criteria for similarity, the applicant proposes to assess consistency in the distribution of each of the Novel BMs in healthy Japanese and non-Japanese adult subjects in accordance with the Clinical laboratory standards institute document EP28-A3C (CLSI 2010). This document presents an evaluation of a statistically significant difference in a mean test value between subclasses as a method to assess whether or not reference ranges for the subject subclasses (i.e., Japanese and non-Japanese) should be separately calculated. It also describes the Harris/Boyd approach (Clin Chem 1990; 36: 265-70) which is a method to judge whether or not to calculate reference ranges for each subclass based on the results of a comparison between Z statistics and threshold values. According to the Harris/Boyd approach, if Z statistics calculated in the sample sizes of Japanese and non-Japanese subjects (n = 40 and n = 80, respectively) in the study in the above Item 1)

and the HV study, is above a threshold value of 2.12 or a ratio of a standard deviation in each subclass is above 1.5-fold, it is recommended that a reference range be specified for each subclass. Through these procedures, the applicant intends to determine similarity in the reference range.

Furthermore, when defining appropriate specificity as 90% or above, a sample size of 40 subjects may provide a power of > 90% to demonstrate that a point estimate of specificity, based on the Guiding Principles, is at least 94%.

## 2) Clinical study in Japanese patients who were exposed to renal toxic drugs

Applicant has acknowledged the opinions of the PMDA. At present, the study set forth in the above Item 2) will be conducted in a prospective design, but instead of implementing it as an independent study, applicant intends to evaluate the Novel BMs using the samples of multiple studies which were carried out for different purposes. The basic study design, including this aspect, will be similar to the confirmatory phase studies. After obtaining the results of the study set forth in the above Item 1) and the clinical studies (cisplatin study and aminoglycoside study) in the confirmatory phase, the applicant will examine an appropriate study design and request a consultation with PMDA on the study design described in the above Item 2).

## (3) Discussion at the consultation meeting and what need to be discussed in future.

The PMDA commented on the clinical study in healthy Japanese subjects as follows:

The PMDA considers that to determine similarity based on the absence of a statistically significant difference in the mean value between the subclasses is inappropriate with regard to the presented criteria for similarity. In addition, the assessment of similarity in the reference range between the subclasses based on the results of a comparison between Z statistics and threshold values, whether or not the use of the presented method for evaluating similarity is appropriate is unclear because it is not a method to directly assess similarity in the reference range between the subclasses. Threshold values based on the Harris/Boyd approach are suggested based on examination of results when the sample sizes of the two subclasses are equal, and the sample sizes between the subclasses (Japanese and non-Japanese) to be compared are different at this time. Therefore, the PMDA, in principle, believes that it is appropriate to examine acceptable specificity and define criteria for the evaluation based on confidence intervals. For instance, it may be an option to judge similarity based on the lower limit of the confidence interval for specificity in Japanese subjects being above the threshold value by defining specificity of

80% as the threshold value in reference to a hypothesis in the overseas confirmatory phase studies. However, the PMDA understands that it is necessary to take feasibility into account when setting the criteria for similarity and the sample size.

Applicant answered that they would consider the suggestions.

### 3. Overall comment on development of Novel BMs

The PMDA commented as follows:

While the clinical usefulness of the Novel BMs and the proposed appropriateness of their usage are unknown at this point, to investigate whether or not the Novel BMs can be used in various regions and ethnic groups would be important for developing drugs utilizing the Novel BMs and clinically adopting them in multiple countries and regions. Thus, the PMDA expects the applicant to actively perform an examination aimed at the implementation of the bridging studies of the Novel BMs in Japanese subjects and recommends holding another consultation on pharmacogenomics/biomarkers to discuss the qualification of the Novel BMs in a timely manner when the results of the clinical studies, which are ongoing or will be conducted in Japan and/or foreign countries to evaluate the Novel BMs, are obtained.

Applicant acknowledged the PMDA's suggestions.