Administrative Notice
March 29, 2011

To: Pharmaceutical Affairs Section, Prefectural Health Department (Bureau)

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Questions and Answers (Q&A) on the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure"

The revision of the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure" was notified by PFSB/ELD Notification No. 0329-18, issued by the Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated March 29, 2011. Questions and Answers (Q&A) on the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure" have been compiled as shown in the Appendix. Please consider informing relevant parties under your jurisdiction of this matter.

Appendix Q&A on the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure"

Common to Acute Heart Failure and Chronic Heart Failure

Q1

It is interpreted that in the development of acute-heart-failure drug/ chronic-heart-failure drug, the superiority of the test drug to placebo alone needs to be demonstrated at any stage before undertaking a Phase 3 study. Is it possible to perform such an evaluation in this field? In addition, if placebo is not adopted as the comparator in a Phase 3 study, how can we demonstrate that the test drug is more useful than placebo?

A1

The superiority of the test drug to placebo alone needs to be shown at any stage before undertaking a Phase 3 study.

It is not always required to demonstrate efficacy using a hard endpoint in the target patient population, for which the test drug is assumed to be actually indicated in clinical practice, as the study subjects. By appropriately selecting the study subjects and efficacy endpoints, the superiority of the test drug to placebo alone can be shown.

Q2

In the development of acute-heart-failure drug/ chronic-heart-failure drug, if clinical studies suggested in the Guidelines are conducted, opportunities for subjects in the control group to receive therapies of which effects to reduce symptoms or improve prognosis have been demonstrated may be restricted; thus, ethical concerns may arise. Consideration should be given so that all subjects can receive the most effective background therapy (optimal standard of care).

A2

As mentioned in the section of concomitant medications, standard therapies for heart failure can be used. Thus, consideration is given to ensuring that all subjects can receive the background therapy (optimal standard of care). It is found that the subject will not be restricted in the opportunity to receive therapies that have been established to reduce symptoms or improve prognosis.

Q3

Subjective symptoms are included in efficacy endpoints in the development of acute-heart-failure drug/chronic-heart-failure drug. How should the improvement of subjective symptoms be assessed?

A3

As for the method of evaluation of subjective symptoms, no standard method has been established at this point in time; therefore, this should be consulted case-by-case basis.

Q4

How should the quality of life (QOL) be assessed in the development of acute-heart-failure drug/chronic-heart-failure drug?

A4

At present, it cannot be said that the standard method for assessing QOL has been sufficiently established. Therefore, this should be consulted case-by-case basis.

ACUTE HEART FAILURE

Q5

For acute heart failure, it is considered unethical, in principle, to use placebo as the comparator, and standard heart failure drugs should be used. What do you think about this?

A5

The placebo group can be established by using an approach, for example, to design a study to investigate an add-on effect of the concomitant use of an existing standard heart failure drug. Also, it is found to be basically necessary to set up the placebo group.

CHRONIC HEART FAILURE

Q6

Please show an applicable example of the case where defining morbidity (e.g., hospitalization or changes of background therapy) as the primary endpoint in a Phase 3 confirmatory study of an chronic heart failure drug is acceptable as a realistic measure.

A6

When the improvement of prognosis has been demonstrated in non-Japanese subjects, and the overseas study results can be used for Japanese subjects, it may be acceptable to select the morbidity (e.g., hospitalization or changes of background therapy) as the primary endpoint in a Japanese Phase 3 confirmatory study as a realistic measure.

Of note, when the improvement of prognosis has not been shown in Japanese or non-

Japanese subjects, only assessment of the morbidity may be insufficient in a Japanese Phase 3 confirmatory study. Nonetheless, even in such a case, approval may be considered if prognosis does not deteriorate, a tendency for improvement in morbidity is demonstrated, as well as the amelioration of QOL is achieved in a Japanese clinical study. However, if the improvement of QOL is not attributable to that of exercise tolerance, the test drug may not be recognized as an heart failure drug.

Q7

With regard to the evaluation of the effect of drugs on prognosis in Phase 3 studies of chronic heart failure drugs, if the results of a clinical study assessing the improvement of morbidity in Japanese subjects shows the same tendency as that in non-Japanese subjects, and efficacy in the Japanese subjects can be adequately explained including other secondary efficacy endpoints, is it deemed that the effect of the drug on prognosis has been fully examined?

A7

The reason for considering approval is not necessarily that the effect of the drug on prognosis has been sufficiently investigated. For instance, in the case where the improvement of prognosis is demonstrated in non-Japanese subjects, even if the conduct of a clinical study of a scale that allows investigation of statistically significant improvement in morbidity is unfeasible in Japan, if the results of the clinical study evaluating the improvement of morbidity for Japanese subjects at least show the same tendency as that for non-Japanese subjects, and if efficacy, including other secondary efficacy endpoints, in Japanese subjects can be fully explained, approval may be considered. Hence, this should be consulted case-by-case basis.

Q8

Please clarify the positioning of QOL in the development of chronic heart failure drugs.

A8

The improvement of QOL is a treatment goal for chronic heart failure as with the improvement of prognosis. However, the amelioration of prognosis takes priority over the improvement of QOL.

Q9

What is the standard questionnaire used for QOL assessment for patients with chronic heart failure?

A9

There is no questionnaire with sufficient use experience in clinical studies that is judged to be a standard at present. This should be consulted case-by-case basis.