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To: Directors of Prefectural Health Departments (Bureaus)

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

Revision of the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure"

With regard to guidelines for clinical evaluation methods for anti-heart failure drugs, the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure", PAB/ELD 1 Notification No. 84 of the Evaluation Division 1, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare dated October 19, 1988 (hereinafter referred to as the "current guidelines") have been notified and used as a standard method for evaluating anti-heart failure drugs in clinical studies that are conducted for the purpose of filing their approval applications. More than 10 years have elapsed since the notification of the current guidelines, and meanwhile, there have been major changes in the status of development/review of anti-heart failure drugs. Therefore, the current guidelines have been revised as presented in the Appendix and will be handled as described below. Please consider informing relevant parties under your jurisdiction of this matter.

Notice

1. Date of Application

   (1) The Guidelines will become applicable on April 1, 2012.

   (2) With the enforcement of the Guidelines, the current guidelines will be abolished as of March 31, 2012.

   (3) After the date of this notification, it is acceptable to adopt the methods and other relevant matters described in the Guidelines in the development plans to the extent possible.

2. Points to consider

   It is not necessarily required to adhere to the methods provided herein as long as they are based on reasonable grounds reflecting, for example, scientific progress.

(Appendix)

Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure

I INTRODUCTION

The Guidelines outline standard methods for conducting clinical studies to investigate the clinical usefulness of new drugs developed for the treatment of heart failure. The Guidelines are a revision of the "Guidelines for Clinical Evaluation of Drugs for the Treatment of Heart Failure" (PAB/ELD 1 Notification No. 84 dated October 19, 1988; hereinafter referred to as the "former guidelines") based on medical and pharmaceutical knowledge because the concept of heart failure has changed significantly over time and the purpose of treatment has altered from the "improvement of cardiac function" in 1988 to "amelioration of patients' quality of life (QOL) and survival rate" at present.

1. Purpose of the revision of the Guidelines

More than 20 years have passed since the establishment of the former guidelines in 1988. The former guidelines do not always reflect the latest medical and pharmaceutical evidence. The duration of clinical studies (observation period) of heart failure drugs was extremely short at the time when the former guidelines were issued: they state that the study duration should be "generally for a few hours to 72 hours for acute heart failure and for at least 4 weeks (usually 3 months) for chronic heart failure". However, there is an opinion that the efficacy and safety of heart failure drugs need to be evaluated for a longer period of time. In the Guidelines, the contents of the former guidelines have been revised based on the current medical and pharmaceutical standards.

In recent years, several issues related to clinical studies of heart failure drugs have been under discussion. In Western countries, for example, there is no expectation of significant effects, except for the improvement of survival rates, in terms of endpoints. Because deaths from heart failure are less common in Japan than in Western countries, it has become necessary to examine whether the survival rate should be selected as an endpoint and how the improvement of QOL should be positioned in clinical studies to be conducted in Japan. These issues have been also reviewed from the biostatistical perspective and incorporated in the Guidelines.

The planning and implementation of clinical studies with reference to the Guidelines may lead to improved reliability of clinical study data in Japan and eventually to the prompt supply of effective and safe drugs to the Japanese people.

In order to revise the guidelines with the abovementioned concept, clinical study plans with scientific rigor, such as specifying appropriate endpoints suitable for the conditions in Japan, are described while taking into account reviews on previously published clinical studies of heart failure drugs, the revision of the former guidelines, and the ethical aspects of drug efficacy evaluation.

II NONCLINICAL STUDIES

In the nonclinical program, it is necessary to conduct pharmacological studies (including hemodynamic studies in appropriate animal models of heart failure) that can appropriately evaluate the efficacy profile in light of the assumed clinical positioning of the drug as well as other studies to investigate the safety profile (toxicity, safety pharmacology, and pharmacokinetic studies). The timing of toxicity, safety pharmacology, and pharmacokinetic (PK) studies is specified in notifications including the “Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals” (PMSB/ELD Notification No. 1019 dated November 13, 1998) and the “Revision of 'Maintenance of the ICH Guideline on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals'” (PMSB/ELD Notification No. 1831 dated December 27, 2000) based on the agreement with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). However, it may be necessary to implement new studies based on safety information obtained from clinical studies. The details of the studies to investigate the safety profiles required by the regulatory authorities will be continuously revised based on the discussion and agreement by the ICH; thus, the studies need to be carried out in accordance with the latest guidelines for nonclinical studies and other relevant rules as necessary.

Information from these studies should be consulted in not only estimating doses for humans but also specifying monitoring of adverse events in clinical studies.

In addition, it is not mentioned in the Guidelines, but the conduct of studies on the quality and specifications of drug substances and products may be also required.

III ACUTE HEART FAILURE

1. Concept of acute heart failure and conditions required for approval for drugs for the treatment of acute heart failure (acute heart failure drugs)

1) Concept of acute heart failure

Acute heart failure is defined as “the onset of symptoms or signs of congestion or low output based on increased ventricular filling pressure or perfusion failure in major organs resulting from organic or functional abnormalities of the heart and a rapid disruption of pumping function of the heart”. Acute heart failure is classified into two types of clinical conditions: The new onset such as acute myocardial infarction and acute exacerbation of chronic heart failure such as dilated cardiomyopathy. The cause of heart failure is primary or secondary myocardial disorder. This leads to damage to the systolic, diastolic, and rhythm functions of the heart that results in systemic dysfunction due to reduced cardiac output or circulatory disorder.

2) Clinical conditions of acute heart failure

Acute heart failure is classified into the following six clinical conditions: (1) Acute decompensated heart failure: New acute heart failure for which signs and symptoms of heart failure are mild and which does not meet diagnostic criteria for such as cardiogenic shock, pulmonary edema, or hypertensive acute heart failure, or chronic heart failure with a distinctive change in clinical conditions; (2) Hypertensive acute heart failure: Signs and

symptoms of heart failure caused by high blood pressure often with a chest radiograph compatible with acute pulmonary congestion and pulmonary edema; (3) Acute cardiogenic pulmonary edema: Pulmonary edema confirmed by chest radiography, which is characterized by respiratory distress and orthopnea with moist rales over the lung fields. Arterial oxygen saturation is often less than 90% before treatment; (4) Cardiogenic shock: A serious pathological condition secondary to tissue hypoperfusion due to marked impairment of microcirculation of peripheral and systemic major organs induced by cardiac pump failure; (5) High-output cardiac failure: Usually it is caused by underlying disease such as thyrotoxicosis, anemia, shunt disease, beriberi heart, Paget's disease, and iatrogenic disease, with warm peripheries, pulmonary congestion, and sometimes noted in septic shock; and (6) Acute right heart failure: It is characterized by low output syndrome with increased jugular venous pressure and hypotension with hepatomegaly.

3) Therapeutic goals and modalities of clinical studies for acute heart failure

The treatment goals for acute heart failure are improvement of subjective symptoms and objective findings, hemodynamics, short-term survival, and QOL. Clinical studies in patients with acute heart failure need to assess the degree of achievement of the abovementioned treatment goals. For primary endpoints in Phase 3 studies, survival, all-cause mortality, cardiovascular morbidity, and subjective symptoms are considered to be appropriate, whereas improvements in hemodynamics, QOL, etc. may play an auxiliary role in efficacy evaluation. Various subjective symptoms, objective findings, hemodynamic parameters, and short-term prognosis are useful indicators for assessing the acute effects of test drugs. Observation time points should be specified according to the characteristics of each test drug, such as on admission, at discharge from the intensive-care unit (ICU), at discharge from the hospital, and after discharge. Appropriate endpoints should be selected by classifying the time points: for predose (e.g., 2 hours to immediately before), early postdose (e.g., 0 to 48 hours to 2 weeks) and long-term postdose (e.g., equivalent to 2 to 4 weeks postdose).

The study subjects are patients with acute heart failure (including acute exacerbation of chronic heart failure). It may be appropriate to evaluate the efficacy and safety separately in patients with acute heart failure and patients with acute exacerbation of chronic heart failure. While taking account that the subjects are generally at cardiopulmonary risk, safety and ethical consideration should be adequately given to avoid disadvantages to patients. In principle, placebo should be used as the comparator in clinical studies to investigate efficacy. Nonetheless, if it is inevitable from the safety or ethical reasons, comparative studies may be conducted using placebo while maintaining the existing standard background therapy of acute heart failure or using an existing heart failure drugs as the comparator. However, if a Phase 3 study does not include placebo control, the test drug must have been demonstrated to be superior than placebo before proceeding the Phase 3 study.

Prior to conducting a clinical study, subjects (or their legally acceptable representatives, if necessary) must be fully informed of the significance of the clinical study, safety and efficacy of the study, and that no disadvantage will occur to them even if the patients do not participate in the study, and the study shall be implemented after they have understood the explanation and provided written consent.

4) Prognosis of acute heart failure and concept of QOL

Clinical studies in patients with acute heart failure should investigate (1) whether short-term survival can be achieved; (2) a reduction in the patients' burdens including subjective symptoms; and (3) a reduction in the severity of impairment at or after hospital discharge (long-term prognosis). Especially, based on the characteristics of acute heart failure, it is important to examine whether short-term survival can be achieved.

Specifically, essential efficacy endpoints in clinical studies involving patients with acute heart failure are clinical signs and symptoms, hemodynamics and prognosis. Indicators of clinical signs and symptoms include respiratory distress, rales, and third heart sound. Hemodynamic parameters include body weight, urine volume, pulmonary capillary wedge pressure (PCWP), brain natriuretic peptide (BNP) and echocardiographic parameters. A hemodynamic assessment should be considered separately from cardiac function. Plasma BNP has been recognized to be important as a predictive factor for the diagnosis and treatment of heart failure, but its significance as an index for evaluating the efficacy of heart failure drugs has not been established. As for prognosis, it is necessary to evaluate both short-term prognosis such as achievement of short-term survival in the acute phase and long-term prognosis such as mortality at 6 months after discharge. Mortality and morbidity need to be assessed. Their indicators include whether life-saving is achieved, time to recovery of spontaneous breathing, time to discharge from ICU, time to discharge from the hospital, recurrence of cardiac accidents after discharge, and hospital readmission. Information on mortality during hospitalization, at 1 month and at 6 months or later after the onset of acute heart failure should be collected to evaluate effects on short-term and long-term life prognoses even after the completion of the test drug administration. In addition, since renal function is anticipated to greatly affect the prognosis, information on renal function should be also gathered at the same time. Furthermore, it is preferable to assess improvement in QOL as well. While standard endpoints for activities of daily living (ADL), cognitive function or QOL related to acute heart failure have not yet been established, there is no objection against the importance of these indices in the aging society.

5) Conditions required for approval for acute heart failure drugs

In order for test drugs to be approved as acute heart failure drugs, it is necessary to demonstrate their efficacy in clinical studies using a primary endpoint for the survival in the acute phase, including mortality and morbidity. Also, it is necessary to show that the test drugs do not worsen not only the prognosis during the acute phase but also the long-term prognosis for at least 6 months (It is not necessarily required to demonstrate improvement in long-term prognosis.).

In addition, clinical studies should reveal the improvement of acute clinical signs and symptoms.

Hemodynamic assessment should be as necessary performed in a timely manner in the development stage. Nonetheless, demonstration of acute hemodynamic improvement alone is considered insufficient because improvement in hemodynamic parameters does not necessarily correlate with that of survival rates. For example, it is inadequate to demonstrate only a reduction in PCWP; thus, either a decrease in the mortality or improvement of clinical signs and symptoms with hemodynamic background such as amelioration of respiratory distress secondary to lung congestion needs to be displayed.

If hemodynamic improvement is revealed in a Phase 2 study, its assessment is not essential in a Phase 3 study; however, at least, it should be shown that there is no deterioration in hemodynamics.

IV CHRONIC HEART FAILURE

1. Concept of chronic heart failure and conditions required for approval for drugs for the treatment of chronic heart failure (chronic heart failure drugs)

1) Concept of chronic heart failure

Chronic heart failure is a long-term condition in which the systolic, diastolic, and rhythm functions of the heart are impaired due to some abnormality of the myocardium and systemic dysfunction caused by decreased cardiac output or congestion of organs due to circulatory disorder. The severity or mode of myocardial abnormalities varies according to causes such as ischemic or metabolic, inflammatory changes in addition to the structural or functional abnormalities of myocardial components. Cardiac failure induced by any factors, however, has common characteristics regardless of causes. Nonetheless, even if cardiac dysfunction based on myocardial abnormality is present, symptoms of heart failure do not always manifest. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for the management of chronic heart failure in adults (revised in 2005) propose a classification system for heart failure stages (A to D). The guidelines define heart failure as the condition that progressed to Stage C or higher and state that heart failure drugs are applicable to Stage C or higher and may be used for Stages A and B only for the prevention of heart failure.

2) Clinical conditions of chronic heart failure

While chronic heart failure is often progressive, the degree of myocardial damage is not necessarily consistent with the severity of heart failure symptoms. It is because the symptoms of heart failure are greatly affected by not only cardiac function but also the function (condition) of organs in the whole body. Therefore, attention should be paid that even if the degree of cardiac dysfunction remains unchanged, the severity of heart failure greatly changes according to the general condition and intervention (treatment); it should be noted that heart failure is reversible.

In the past, heart failure based on systolic dysfunction has been considered to be a target pathology of heart failure drugs among cardiac functional disorders. In clinical studies of heart failure drugs, mostly patients with past or current evidence of heart failure with a left ventricular ejection fraction (LVEF) of $\leq 35\%$ were included. In such patients with systolic heart failure, the activation of neurohumoral factors and myocardial remodeling (e.g., heart enlargement and ventricle becoming a spherical shape) have been identified to be factors to accelerate the progress of the disease. Myocardial remodeling (especially cardiac hypertrophy/myocardial fibrosis), myocardial ischemia, and electrolyte abnormalities are factors that promote fatal arrhythmia. However, biomarkers to predict sudden death have not been established.

In the Vasodilator-Heart Failure Trial (V-HeFT) and Digitalis Investigation Group (DIG) study, heart failure patients with a LVEF of $\geq 50\%$ were included in the subjects. An epidemiological study revealed that heart failure with preserved ejection fraction (HF-

pEF) or diastolic heart failure accounted for 40 to 50% of all patients with heart failure and that there were many elderly female patients and those with past or current evidence of hypertension. In addition, it has been also known that renal impairment, anemia and diabetes mellitus are common comorbidities. However, this diastolic heart failure is not a disease type of systolic heart failure in its course of progression, but diastolic and systolic heart failures are found to be individually independent diseases. If the pathology is elucidated in the future, it may be necessary to consider the indications for treatment separately for systolic heart failure and diastolic heart failure.

3) Therapeutic goals and modalities of clinical studies for chronic heart failure

Treatment goals for chronic heart failure are (1) improvement in prognosis, (2) maintenance of the ability to sustain social and family life (improvement of morbidity), and (3) improvement of subjective symptoms and maintenance of comfort in life. Therefore, it is necessary to evaluate the achievement level of the abovementioned treatment goals in clinical studies involving patients with chronic heart failure. For primary endpoints, all-cause mortality, cardiovascular morbidity, and subjective symptoms are found to be appropriate; QOL, exercise tolerance, physical findings, changes in hemodynamics (e.g., EF), renal function, and neurohumoral factors are likely to play auxiliary roles as secondary endpoints in efficacy evaluation. Evaluation methods for QOL are subsequently described. The improvement of subjective symptoms should be assessed for a period of at least 6 months.

Since study subjects are patients with chronic heart failure who have a poor prognosis and impaired QOL, sufficient consideration should be given to the safety and ethics to avoid disadvantages to patients in conducting the clinical study.

A phase 3 study may be a placebo-controlled study or comparative study using an existing heart failure drug as a comparator while maintaining the current appropriate background therapy for chronic heart failure, but it should be designed as a randomized double-blind comparative study. However, if placebo is not adopted as the comparator in a Phase 3 study, the treatment drug should be demonstrated to be more useful than placebo at any stage before starting the Phase 3 program by using any means.

For many drugs, a study including death (mortality) as the primary endpoint is likely to be required before approval, regardless of the details of proposed indications. When drugs have new mechanisms of actions or drugs in the same class have been shown to adversely affect mortality, death examined in a prospective randomized, controlled study is necessary.

For chronic heart failure, death has been internationally defined as the primary endpoint. However, the implementation of Phase 3 studies with death as the primary endpoint may be often difficult in Japan where the mortality of heart failure is low. Moreover, there is no appropriate endpoint substituting death; therefore, defining morbidity (e.g., hospitalization or changes of background therapy) as the primary endpoint may be an acceptable realistic measure for Japanese Phase 3 studies. Alternatively, if participation in a large-scale global clinical study with death as the primary endpoint is judged to be feasible as a Phase 3 study, this global clinical study can be positioned as a confirmatory study.

In the development of chronic heart failure drugs, when taking part in a large-scale global Phase 3 study, attention should be paid to the following points: Because it is an area in

which there may be differences in dosage and administration based on ethnic differences between Japanese and non-Japanese subjects, a Phase 2 study to determine a dose for Japanese subjects is usually required prior to participation in the global Phase 3 study. At least, it is necessary to demonstrate that doses to be investigated in the global Phase 3 study are appropriate for Japanese subjects beforehand. When the dosage regimen cannot be narrowed down to one dose based on Japanese and overseas Phase 2 studies, a development policy to perform a global Phase 3 study with multiple doses such as two dose levels (high and low) and examine approved doses for each country according to the results can be adopted.

If it is difficult to evaluate prognosis in the Phase 3 program, a prognosis should be investigated in post-marketing clinical studies whenever possible. The observation period should be set to one year or longer in consideration of the type, characteristics, etc. of investigational drugs.

Prior to the conduct of a clinical study, the significance and expected safety of and benefits from the study shall be fully explained to subjects, and the study shall be implemented upon the subjects' understanding and written informed consent.

4) Prognosis of chronic heart failure and concept of QOL

It has been shown that prognosis and QOL of patients with chronic heart failure do not always correlate with each other. The prognostic factors of chronic heart failure are organ failure due to cardiac pump failure and sudden death, which account for 40% to 50% of cardiovascular deaths. The incidence of sudden death does not correlate with QOL, and it frequently occurs in a patient group with good QOL. The QOL of patients with chronic heart failure is determined based on both physical (ability to exercise) and mental aspects. While exercise tolerance is defined by maximum exercise capacity and expressed by peak VO_2 in cardiopulmonary exercise testing, a 6-minute walk distance is commonly used as a simplified procedure. The specific activity scale (SAS) is also a measure of exercise capacity in daily living but does not reflect maximal exercise capacity. In contrast, QOL is based on self-assessment by individual patients. Subjective evaluation is usually obtained from answers to questions so that some questionnaires for assessment of QOL in patients with chronic heart failure are proposed and used for this purpose.

The treatment goals for patients with chronic heart failure are to improve a prognosis first and then QOL. Therefore, the requirements for heart failure drugs in the treatment of chronic heart failure are not primarily focused on improvement of heart failure symptoms leading to the amelioration of QOL, and improvement of prognosis should be prioritized to the amelioration of QOL.

5) Evaluation of therapeutic drugs that affect life prognosis

For the prognosis of chronic heart failure, the 5-year survival rate has been reported to be 50% to 60%[1], but there is no difference between the 1-year and 5-year prognoses. However, several clinical studies in patients with chronic heart failure showed differences between 6-month and 1-year prognoses so that a long-term prognosis should be followed for at least one year. Analysis of prognosis requires a scientifically justified sample size and investigation according to the protocol. Since there is no surrogate for deaths, either all-cause deaths or cardiovascular deaths should be included in the primary endpoint. Hospitalization due to deterioration of heart failure can be adopted as an index

for morbidity, but because heart failure is a reversible condition, it cannot be used as a surrogate measure for mortality. It should be noted that the clinical importance of mortality as an endpoint varies from that of morbidity. However, hospitalization due to deterioration of heart failure and changes or additions of treatment for worsening of heart failure are in the same nature even if their severity varies; thus, they can be handled as indexes for morbidity.

6) Evaluation of therapeutic drugs that affect QOL

Improvement of QOL in patients with chronic heart failure is classified into the following based on the cause: (1) improvement of the condition of heart failure, (2) improvement of exercise tolerance, and (3) mental/ psychological improvement.

Improvement of QOL based on the amelioration of the condition of heart failure is achieved when symptoms of heart failure improve as a result of the amelioration of either organ failure due to cardiac pump failure or organ congestion. Improvement in organ blood flow associated with increased cardiac output ameliorates organ failure as well as QOL. Decreases in lung or liver congestion or leg edema also contribute to the improvement of QOL. However, improvement in the condition of heart failure may not ameliorate the QOL.

The improvement of exercise tolerance is an important factor for amelioration of QOL. Exercise tolerance is determined based on the volume of blood supplied to exercising skeletal muscles during the maximum exercise, and parameters for oxygen ventilation in the lungs are rarely used as predictors. Exercise tolerance represents the maximum oxygen utilization capacity of the skeletal muscles so that not only drugs increase blood flow to exercising skeletal muscles, such as cardiotonics and vasodilators, but also drugs enhancing the oxygen uptake and utilization rate by skeletal muscles improve exercise tolerance.

Mental and psychological aspects are major determinants of QOL. However, physical factors often influence mental factors. Thermotherapy, exercise therapy, and change of environment therapy may include such effects. Some drugs may have direct psychotropic effects, such as selective serotonin reuptake inhibitors (SSRIs) and sleep-improving drugs. In addition to drugs, it is needless to say that the support from and communication with family members and healthcare providers greatly contribute to the improvement of QOL.

For evaluation of QOL, many questionnaires have been prepared across the world. The quantitative evaluation on the efficacy of heart failure drugs is mainly made based on questions concerning the physical domain. There is no clinical study that has shown a significant therapeutic effect for questions concerning the emotional domain.

7) Conditions required for approval for chronic heart failure drugs

The objectives of chronic heart failure drugs are to improve patients' prognosis and QOL. It is most desirable if both are satisfied. When the improvement of the two elements is inconsistent, the improvement of prognosis is prioritized over the improvement of QOL. Therefore, if prognosis improves, the approval for the drugs is considered even if they do not improve QOL. However, when QOL markedly deteriorates (e.g., patients require bed rest , frequent complaint of dyspnea, etc.), the drugs may not be approved depending on their details, severity and/or incidence, or can be approved with conditions.

In contrast, when prognosis does not improve or deteriorate, approval is considered by viewing the drugs as useful for the treatment of chronic heart failure as long as QOL improves. However, when the improvement of QOL does not result from the amelioration of exercise tolerance, it should be noted that they may not be defined as heart failure drugs. The drugs are not approved if they do not improve prognosis or QOL.

When the long-term prognosis deteriorates, the drugs should not be approved as heart failure drugs even if they improve QOL. Nonetheless, approval with conditions may be considered if the worsening of prognosis is limited to a specific subgroup, factors identifying the subgroup are evident, and QOL clearly improved in other subgroups.

A large-scale clinical study is usually required to evaluate prognosis. If a sufficient number of subjects cannot be ensured in Japan, overseas data can be extrapolated and used for Japanese application review, but intrinsic and extrinsic factors need to be examined for the use of overseas data (see "Ethnic Factors in the Acceptability of Foreign Clinical Data" [PMSB/ELD Notification No. 672 dated August 11, 1998] and "Basic principles on Global Clinical Trials" [PFSB/ELD Notification No. 0928010 dated September 28, 2007]). Chronic heart failure treatment is considered to be a clinical field in which ethnic differences based on intrinsic factors and extrinsic factors such as the medical environment are large. Particularly, it is necessary to sufficiently investigate differences in the dosage and administration of the test drug between Japan and overseas, differences in severity, etc. of study patients, and differences in background therapies. With regard to the doses of a test drug, if the dose is expected to show efficacy equivalent to that in non-Japanese subjects using endpoints based on pharmacokinetic/pharmacodynamic (PD) study results as a standard dose for Japanese subjects, it may be concluded that the equivalent effect on prognosis between Japanese and non-Japanese subjects can be anticipated. When a dose lower than the standard dose for non-Japanese subjects expected to show equivalent efficacy is selected as a standard dose for Japanese subjects, attention should be paid to the use of overseas studies. For background therapy drugs, it is presupposed that there is no marked difference between Japanese and non-Japanese subjects. The contents (including the types, dosage and administration, etc. of investigational drugs) of the standard therapy for chronic heart failure in overseas studies should be reviewed in detail, and their comparison between Japan and foreign countries as well as their impact on the efficacy and safety of the test drug need to be examined. For drugs approved by extrapolation of overseas data, it is recommended to conduct post-marketing surveillance (including post-marketing clinical studies).

The evaluation on morbidity in Japan is likely to be an essential requirement for approving chronic heart failure drugs. When the improvement of prognosis has been demonstrated in foreign countries and the said overseas study data are usable for Japanese subjects, approval is considered as long as the drugs improved morbidity in Japan. Even if the conduct of a clinical study of a scale that allows investigation of statistically significant improvement in morbidity is unfeasible in Japan, it is at least necessary to show that the results of the clinical study evaluating the improvement of morbidity for Japanese subjects have the same tendency as that for non-Japanese subjects. In addition to this, if efficacy, including other secondary efficacy endpoints, in Japanese subjects can be fully explained, approval may be considered. In the future, if factors for which the causal relationship with prognosis are identified, and efficacy in Japanese using these as alternative endpoints is demonstrated, drugs may be approved. At present, however,

factors corresponding to such have not yet been established. (Biomarkers such as BNP, improvement of ventricular remodeling confirmed by imaging diagnosis, amelioration of fatal arrhythmia, improvement of body fluid volume, etc. are anticipated to be parameters to be studied.)

In the development of chronic heart failure drugs, the evaluation of QOL (physical and mental aspects) needs to be performed in Japan because there are large differences in the medical environment (e.g., conditions for inpatient care, the actuality of outpatient treatment, use status of drugs, etc.) and living environment, and cultural differences in the values regarding life cannot be ignored. In particular, long-term improvement of symptoms is an important endpoint. As mentioned previously, approval is considered for drugs that improve QOL, as those useful for the treatment of chronic heart failure. However, it is premised that at least the drug should achieve a tendency for improvement of morbidity and should not cause worsening of prognosis.

V CLINICAL STUDIES OF DRUGS FOR THE TREATMENT OF HEART FAILURE (HEART FAILURE DRUGS [ACUTE OR CHRONIC])

The objectives of clinical studies are to comprehensively evaluate the efficacy and safety of test drugs in healthy adult and patient populations and to examine the clinical usefulness of the test drugs. Clinical studies can, however, be undertaken only when investigational drugs are expected to be effective within the scope of acceptable safety in humans based on nonclinical study data.

Clinical studies shall be conducted in accordance with the spirit to respect human rights such as the Declaration of Helsinki and procedures set forth in the Good Clinical Practice (GCP). In the first stage (Phase 1 studies), safety and pharmacokinetics (PK) in healthy adult subjects should be investigated. In the second stage (Phase 2 studies), safety, efficacy, dose response and other relevant matters should be evaluated in a small number of patients with heart failure expected to respond to the test drug. In the third stage (Phase 3 studies), based on their results, the usefulness and safety should be exhaustively examined using an appropriate sample size of patients with heart failure, who are the target population of the test drug in actual clinical practice, in the light of the study objectives. At any stage, if any efficacy or safety question arises, reexamination shall be made starting from previous stages including nonclinical studies. In principle, whether or not to grant approval is reviewed based on Phase 3 study results. However, even after the drug is provided to clinical practice, surveys to detect unexpected adverse events (AEs) and adverse drug reactions (ADRs), which are not identified in the previous stages, will be performed, and as necessary, the implementation of a post-marketing clinical study as the fourth stage (Phase 4) will be considered.

Phase 2 and subsequent studies directly involve patients with heart failure. Prior to the initiation of each clinical study, all results on the concerned test drug, which became available from studies up to the previous phase, should be examined from multilateral and various perspectives, the goals of heart failure treatment most suitable for the test drug should be selected, and the study subjects, clinical study method, parameters and assessment methods for pharmacological efficacy, and other relevant matters should be determined.

1. Phase 1 studies

In a Phase 1 study, a treatment drug is administered to humans for the first time. In this stage, the primary objective is to find a safe dose and dosage regimen of the treatment drug. The characteristics of the test drug in humans using placebo as the comparator are investigated. In particular, special consideration should be given to ensuring safety.

1) Person in charge of the study

   The study will be conducted by a clinician with sufficient knowledge and experience in heart failure drugs in cooperation with the person responsible for nonclinical studies and experts familiar with clinical pharmacology.

2) Subjects

   In principle, the subjects should be healthy adult volunteers and studied in an inpatient setting or setting equivalent to this.

3) Safety evaluation

   The presence or absence of expected or unexpected abnormalities (adverse reactions) should be searched based on subjective symptoms, physical findings and clinical physiological/ laboratory findings.

4) Study method

   (1) Dosage and administration

      a. Single administration
      A starting dose taking account of an adequate safety margin should be selected based on a no-observed-adverse-effect level (NOAEL) confirmed in nonclinical studies and titrated while checking safety.

      b. Repeated administration
      After safety is demonstrated in a single-dose study, repeated administration over an appropriate period should be further attempted while taking into account dosage regimens and doses expected to be used in the future. For oral medications, repeated administration at the maximum safe dose or recommended dose of the drug should be continued until blood concentrations reach steady state. For non-oral formulations such as transdermal preparations, ration the dosing intervals should be determined according to the anticipated PK.

   (2) Endpoints

      a. PK
      Whenever technically possible, the characteristics related to absorption, distribution, metabolism, and excretion of the drug should be clarified to obtain basic information for determining the dose and dosing interval. In other words, items such as the bioavailability, blood half-life, volume of distribution, metabolic organ, elimination pathway in the body and identification of metabolites of the test drug should be evaluated. Furthermore, blood drug concentrations after repeated administration should be assessed at appropriate intervals to characterize the PK properties of the test drug.

b. PD

Endpoints include subjective symptoms, physical findings, urine volume, body weight, body temperature, blood pressure, respiratory rate, heart rate, electrocardiography and echocardiography. Observation should be performed at appropriate intervals. Furthermore, it is desirable to measure as many hemodynamic parameters as possible that represent cardiac function, as appropriate. Also, at least necessary laboratory tests should be performed before and after the study, and if any abnormality is found, an additional investigation or follow-up should be carried out. If the drug is expected to be used for a long period of time, it is desirable to conduct a study to investigate the tolerability of long-term repeated administration.

2. Phase 2 studies

The objectives of Phase 2 studies are to investigate the safety and efficacy of test drugs in patients who are expected to respond to it. For acute heart failure, hemodynamic data from a patient population, which is close to clinical target patients, should be collected for determining a dose, and the study should be designed in such a manner that information including the minimum effective dose, dose increases and maximum treatment duration can be obtained based on PCWP and safety data. Essentially, it is an exploratory study including the selection of dosage and administration, and the contents of the Phase 3 program will be determined based on the Phase 2 studies. Therefore, because the safety information on the test drug has not been sufficiently accumulated at this stage, participation of patients who are likely to experience unexpected events or patients with unstable hemodynamics should be avoided to the extent possible. Safety considerations should always be given priority in the conduct of clinical studies. The sample size, analysis plan and other relevant matters should be appropriately specified in reference to the “Statistical Principles for Clinical Trials” (PMSB/ELD Notification No. 1047 dated November 30, 1998) and other relevant guidelines, and powers suitable for study objectives should be ensured.

1) Phase 2a study

After Phase 1 studies are completed, a Phase 2a study to investigate the safety and efficacy of the test drug should be performed in the target patients. Based on various data obtained prior to its implementation, a Phase 2a study and a subsequently described Phase 2b study may be found to be conducted together in a single study.

(1) Person in charge of the study

A physician who has sufficient clinical experience in heart failure and is familiar with pharmacological evaluation of heart failure drugs should be responsible for this study.

(2) Subjects

The subjects should be patients with heart failure who are expected to respond to the test drug. In principle, young children, pregnant women, women very likely to become pregnant and very elderly patients should not be included in the study. It is desirable to conduct the Phase 2a study in inpatient settings from the viewpoint of safety management.

(3) Dosage and administration

The study should be implemented with the dosage and administration judged to be appropriate based on Phase 1 study results.

(4) Duration of the study

The administration of test drugs should be started after a certain period of observation. The duration of the study should be determined according to the condition of the target patients, and PD/PK profiles of the test drug.

(5) Concomitant medications

Concomitant medications interfering with the evaluation of safety and efficacy of the investigational drug (e.g., drugs that show interactions with existing heart failure drugs or other therapeutic agents) makes the interpretation of results difficult and should be avoided whenever possible. However, because the subjects are patients with severe acute heart failure or chronic heart failure with a poor prognosis, evidence-based standard therapy, such as digitalis, diuretics, angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, β-blockers, and aldosterone antagonists, may be continued without changing their dosage and administration. The details of standard therapy (e.g., types and doses of the treatment drugs) should be specified in the protocol before study initiation.

(6) Endpoints

Examples of major endpoints to be observed for acute and chronic heart failure are presented below (to be selected/added according to the nature of the clinical study and the emergence of a new evaluation method):

a. Mortality

b. Subjective symptoms
Generalized malaise, fatigability, exertional dyspnea, orthopnea, angina (-like) symptoms, etc.

c. Physical findings
Body weight, heart rate, arrhythmia, blood pressure, respiratory rate, pulmonary rales, edema, hepatomegaly, jugular venous distention, additional heart sounds, cardiac murmurs, coldness of limbs, cyanosis, etc.

d. Severity classification of cardiac function
New York Heart Association (NYHA) Functional Classification

e. Chest radiography
Pulmonary congestion, pulmonary edema, and cardiothoracic ratio

f. Electrocardiography/long-term recording electrocardiography
Heart rate, arrhythmia, atrioventricular conduction defect and myocardial ischemic findings, etc.

g. Echocardiography
Intracardiac dimensions, ventricular wall motion, left ventricular fractional shortening (FS), left ventricular ejection fraction (EF), inferior vena cava diameter, tricuspid regurgitation pressure gradient (TRPG), left ventricular inflow pattern (early diastolic wave/atrial

systolic wave [E/A], deceleration time of E wave [DT], isovolumic relaxation period [IRT]), left ventricular early diastolic wave/mitral annulus velocity (E/E'), and the presence of pericardial effusion (M-mode, tomography, Doppler)

h. Nuclear medicine study
Assessment with quantitative Gate SPECT (QGS) using RI cardiac pool scintigraphy and ^{201}Tl myocardial scintigraphy

i. Computed tomography (CT) and magnetic resonance imaging (MRI)

j. Exercise tolerance
Maximum oxygen uptake (PVO_2) by exhaled gas analysis, 6-minute walk test, Specific activity scale (SAS), etc.

k. Blood drug concentrations
It is advisable to measure blood concentrations of the test drug following administration at appropriate intervals and reveal the relationships between the PK/PD of the test drug and the abovementioned parameters.

l. Bioactive tissue and circulating material activity
Natriuretic peptide (plasma BNP and serum NT-pro BNP levels), humoral factors of the renin-angiotensin-aldosterone system, sympathetic nervous system (norepinephrine), vasodilators (bradykinin, nitric oxide, prostaglandin), cytokines (endothelin, tumor necrosis factors, and interferon), vasopressin, matrix metalloproteinase, etc.

m. For acute heart failure, invasive hemodynamic tests
Measurement of arterial pressure, right atrial pressure, pulmonary arterial pressure, pulmonary capillary pressure and cardiac output, calculation of cardiac index, stroke volume, total peripheral vascular resistance, pulmonary vascular resistance, and double product, etc.

n. Others

[1] Urine output (particularly for acute heart failure)

[2] Blood gas analysis (arterial oxygen saturation) (particularly for acute heart failure)

[3] Liver function test, renal function test

[4] Urinalysis, hematology and serum biochemistry

[5] QOL assessment, Mini Mental State Examination (MMSE), etc.

Measurements should be repeated at appropriate intervals, as necessary, to ensure safety.

2) Phase 2b study

The study will be conducted based on an appropriate plan to further investigate the safety and efficacy of the test drug in a larger number of patients and to clarify more detailed indications and dose-response relationships. When there seems to be differences in response according to the types or severity of the underlying disease, heart failure (acute or chronic), there are drugs that are frequently concomitantly used in clinical practice, or

use in patients with concurrent conditions such as kidney disease or arteriosclerosis is anticipated, a protocol taking account these is required. For dose setting, in principle, it may be necessary to establish a placebo group and test drug group at least at two dose levels. The dose-response relationship should be appropriately investigated with reference to the “Dose-response Information to Support New Drug Registration” (PAB/ELD Notification No. 494 dated July 25, 1994) and other relevant guidelines.

(1) Person in charge of the study

As specified for the Phase 2a study.

(2) Subjects

Based on data obtained from the Phase 2a study, the Phase 2b study should be implemented in patients with heart failure with specific hemodynamic conditions on which the test drug is anticipated to be effective (an appropriate number of patients including severe patients). However, if patients with severe heart failure, young children, pregnant women, women who are very likely to become pregnant and very elderly patients are included in the study, special consideration to the study method is required.

(3) Dosage and administration

The study should be implemented with the dosage and administration judged to be appropriate based on Phase 2a study results. It is desirable to design the Phase 2b study as a double-blind, parallel-group, comparative study and investigate a clinical recommended dose. If the maximum dose is higher than a dose experienced up to the previous phase, safety should be newly examined.

(4) Duration of the study

The duration of the study should be determined based on the condition of the target patients, PD and PK profiles of the test drug, and data obtained from the Phase 2a study. In general, at least 3 months are appropriate for chronic heart failure. For acute heart failure, it is usually approximately several hours to 72 hours, but it may be necessary to evaluate the outcome after treatment for a long period up to approximately 4 weeks.

(5) Comparator

It is preferable to use placebo as the comparator. However, an alternative is to select an appropriate standard drug as the comparator from the safety and ethical viewpoints of the clinical study. In a such case, the following two points should be taken into consideration for choosing the standard drug:

a. Has its evaluation been established?
Select from drugs for which clinical evaluation has been established.

b. Is it similar?
Take chemical and pharmacological similarities to the test drug and similarity in clinical indications into consideration as well.

(6) Concomitant medications

As specified for the Phase 2a study.

(7) Endpoints

As specified for the Phase 2a study.

(8) Long-term treatment

In order to demonstrate the usefulness of long-term treatment with the test drug in the treatment of chronic heart failure, patients who can receive long-term treatment and are found to be appropriate should be selected, and they should be treated with the test drug and observed for at least several months. For patients who are scheduled to receive long-term treatment, premature withdrawals, dropouts and the development of resistance should also be adequately evaluated. During the treatment period, the patients should be followed up at appropriate intervals to investigate for abnormalities.

(9) Additional study

When there are symptoms, physical findings, or abnormal changes in laboratory tests or clinical physiological tests in Phase 1 or 2 studies, or actual clinical study results greatly vary from results anticipated from nonclinical study data, an additional study according to objectives needs to be performed to learn the effect of the test drug on the blood, nerves, liver, kidneys and humoral factors such as catecholamine, the renin-angiotensin system and BNP.

3. Phase 3 studies

In a Phase 3 study, an appropriate comparator should be selected, and the efficacy (superiority [or noninferiority]) of the test drug should be verified within the scope of the indications and with dosage and administration of the test drug revealed in the Phase 2 studies. In principle, a Phase 3 study should be designed as an adequately controlled double-blind comparative study. However, for drugs primarily targeting patients with serious heart failure, the first priority should be given to patients' benefits, and the study method (e.g., comparator, endpoints and duration of the study) should be appropriately selected while taking into account the intended use and efficacy of the test drug, and Phase 2 study results. The sample size, analysis plan and other relevant matters should be appropriately specified in reference to the "Statistical Principles for Clinical Trials" (PMSB/ELD Notification No. 1047 dated November 30, 1998), "Basic principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and other relevant guidelines.

1) Person in charge of the study

The study should be carried out by a clinician with profound experience in the treatment of cardiovascular diseases who is selected among multiple sites.

2) Study sites

An appropriate number of patients should be assigned to multiple sites while taking into account differences in the treatment of heart failure among the sites.

3) Subjects

The subjects should be patients with heart failure who are expected to be well indicated for the test drug. However, if young children, pregnant women, women who are very likely to become pregnant and very elderly patients are included in the study, special consideration to the study method is required.

4) Dosage and administration

The dosage and administration determined based on the Phase 2 study results should be followed.

5) Duration of the study

The duration of the study determined based on the Phase 2 study results should be followed. For acute heart failure, it is preferable to assess the mortality during hospitalization, at 1 month and at 6 months or later after the onset of acute heart failure to investigate the effects on short-term and long-term prognoses even after the end of the study. A study period of at least one year is required to evaluate the prognosis of chronic heart failure.

6) Comparator

As specified for the Phase 2b study.

7) Concomitant medications

As specified for the Phase 2a study.

8) Endpoints

As specified for the Phase 2a study. Other endpoints identified as issues in earlier studies, including nonclinical, Phase 1 and 2 studies. Endpoints related to prognosis such as all-cause mortality and cardiovascular morbidity.

4. Phase 4 studies

A Phase 4 study is a clinical study conducted, as necessary, after approval of the drug. In chronic heart failure, it may be desirable to conduct a Phase 4 study in Japan evaluating long-term prognosis for at least one year in some cases, for example, where the effect of the drug on prognosis could not be sufficiently evaluated in a Phase 3 study and approval was granted based on extrapolation of overseas data.

Because heart failure often follows a chronic course, long-term experience of drug is important. It is also necessary to examine the effects of the drug on prognosis and QOL. In addition, the development of drug resistance, ADRs and withdrawal syndrome after discontinuation of the drug should be examined in detail at the same time with the evaluation on the heart failure effect of the drug. While these data may be collected through a post-marketing surveillance, a Phase 4 study should be conducted if data beyond the scope of the surveillance and more robust data are needed. Furthermore, in some cases, it may be preferable to conduct a comparative study (e.g., noninferiority study) using a standard therapy or study in combination with another drug to assess the clinical role of the drug, and additional clinical study to examine the validity of dose selection. The Phase 4 study should evaluate long-term continuous use of an heart failure drug from a relatively broad perspective, including hematological and serum biochemical findings, to confirm safety and clarify the appropriate use of the drug.

VI DESCRIPTIONS ON INDICATIONS

The Guidelines are directly applicable to acute and chronic heart failure. Therefore, clinical studies of heart failure drugs should be conducted in accordance with the Guidelines, and if their usefulness is demonstrated, the indication should be defined as, in principle, “acute heart failure (including acute exacerbation of chronic heart failure)” or “chronic heart failure”.

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