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July 9, 2010

To: Heads of Prefectural Public Health Bureaus (Departments)

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

On release of the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents

This guideline provides the standard procedures to evaluate oral hypoglycemic agents in clinical stages which conducted for new drug application. The guideline will be applied as specified below. Please inform relevant manufacture and marketing authorization holder under your jurisdiction about the application of this guideline.

1. Date of application
   (1) The guideline will be applied as of July 1, 2012.
   (2) After the release of this notification, it is possible to incorporate the procedures specified in this guideline during development of a new drug.

2. Point to be considered
   Strict adherence to the guideline is not intended when other procedures or methods to be employed are based on a rationale, such as one that reflects the latest scientific advances.

[1] This English version of the Japanese Notification is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the Japanese text shall prevail.

(Attachment)

Guideline for Clinical Evaluation of Oral Hypoglycemic Agents

I. Introduction

This guideline provides the currently appropriate methods of and the general procedures for planning, conducting and evaluating in clinical studies to investigate the clinical usefulness of medicinal products newly developed as oral hypoglycemic agents (OHAs).

The goals of diabetes treatment is to maintain patient's quality of life (QOL) as close to the same level as that of healthy people as possible, and attain their healthy life expectancy by preventing development and progress of diabetic complications. In order to achieve the stated goals, various metabolic abnormalities associated with diabetes mellitus must be corrected including glucose metabolism, and OHA is expected to correct such abnormalities primarily in glucose metabolism. The ultimate markers of usefulness of diabetes treatment will be clinical endpoints such as prevention of development and progression of microvascular and macrovascular complications. However, the appropriateness of using the clinical endpoints for evaluation of unapproved drugs in the stage of clinical trials, remains to be further discussed in terms of necessity, methodology, and evaluation methods.

Accumulated evidence supports that optimal glycemic control is effective for prevention of development and progression of diabetic complications. Glycemic control is therefore widely recognized as an efficacy marker for OHA. It is appropriate that evaluation of the efficacy of an OHA should be primarily based on glycohemoglobin (HbA1c), an internationally accepted and stable marker for glycemic control. Since OHA is usually administered to patients for long periods, safety evaluation in long-term treatment is an important part of the evaluation of usefulness. Also, an OHA is generally used concomitantly with other OHAs with a different mechanism of action, and therefore usefulness in concomitant therapies must be evaluated thoroughly especially concerning safety. In addition, OHA is clinically applied to patients with various conditions and thus when conducting a clinical study, actual clinical practice should be adequately reflected. Specifically, elderly patients and high risk patients with complications, who are assumed to use the drug in clinical practice after approval, should be included in clinical studies as much as possible.

This guideline was prepared, in hopes of improving the quality of clinical studies, based on the current diabetes treatment as well as on the idea of how drug therapies for diabetes treatment should be advanced in the future. One should carefully consider patients' benefits and cope flexibly with the guideline, in accordance with experiences, treatment outcomes, scientific evidence and accumulation of new findings. As for development of medicinal products to treat diabetes mellitus other than OHAs, e.g., insulin preparations, this guideline is recommended to be used as a reference.

II. Characteristics of diabetes mellitus

1. Concept of the disorder

   According to the concept of diabetes mellitus provided in "Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus"[1)] published by the Committee of Japan Diabetes Society for the Classification and Diagnostic Criteria of Diabetes Mellitus in 1999, diabetes mellitus is "a group of diseases characterized by chronic hyperglycemia and other specific metabolic abnormalities, with heterogenous etiologies in which both genetic and environmental factors are involved. After a long duration of metabolic derangement, specific

complications of diabetes (retinopathy, nephropathy and neuropathy) may occur. Arteriosclerosis is also accelerated in the presence of diabetes. Depending on the severity of metabolic abnormality, diabetes may be asymptomatic, may present with characteristic symptoms such as thirst, polyuria, polydipsia, weight loss, or it may progress to ketoacidosis and coma."

2. Classification of diabetes mellitus

The mechanism of the onset and pathophysiology of diabetes mellitus need to be understood based on defective insulin secretion and action. Specifically, defective insulin secretion in the pancreatic β cells and defective insulin action in the target organs and tissues such as muscle, liver and adipose tissue increase the blood glucose level and trigger the onset of diabetes mellitus. According to the current classification of diabetes mellitus developed based on the 1999 Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus,[1)] diabetes mellitus is classified based on pathogenesis (mechanism of onset) and pathophysiology (stage).

The terms type 1 and type 2 are used for pathogenetic classification, according to which diabetes mellitus is classified into four types; type 1 diabetes mellitus associated with defective insulin secretion due to pathological destruction of the pancreatic β cells, type 2 diabetes mellitus associated with both decreased insulin secretion and insulin sensitivity, other types of diabetes mellitus triggered by specific causes, and gestational diabetes mellitus.

On the other hand, the pathophysiological (stage-based) classification is a totally different approach, and diabetes mellitus is graded according to the severity of metabolic abnormality and defective insulin action. Accurate classification of diabetes mellitus according to the pathogenesis and understanding of the pathophysiological condition of the patient are both important for determining an optimal treatment strategy.

(1) Type 1 diabetes mellitus

Type 1 diabetes mellitus is triggered by destruction of the β cells. In general, patients with type 1 diabetes mellitus are insulin dependent, requiring insulin in order to survive. Type 1 diabetes mellitus is further classified into autoimmune diabetes mellitus and idiopathic diabetes mellitus. In autoimmune diabetes mellitus, autoantibodies against the islet antigen, e.g., GAD antibody, ICA, anti-insulin antibody and IA2 antibody, are present at an early stage. On the other hand, some patients rapidly become insulin dependent in the same way as patients with autoimmune diabetes mellitus who have no detectable autoantibodies, and the condition is considered to be idiopathic. While the mechanism of pancreatic β cell destruction in idiopathic diabetes mellitus is unknown, a subtype called fulminant type 1 diabetes mellitus has been identified in a recent study.[2)] Some autoantibody-positive patients become insulin dependent slowly progressively over the years.

(2) Type 2 diabetes mellitus

Type 2 diabetes mellitus is characterized by decreased insulin secretion and sensitivity, and most Japanese diabetes patients have type 2 diabetes mellitus. The extent of involvement of insulin secretion and insulin sensitivity is different in individual patients. In some patients type 2 diabetes mellitus may be caused mainly by decreased insulin secretion, while in others it may be caused mainly by insulin resistance resulting in relative insulin deficiency. Insulin dependence is rare in type 2 diabetes since the pancreatic β cell function is maintained at a certain level.

Defective insulin secretion and insulin action are both affected by genetic and environmental factors. Genetic basis of type 2 diabetes mellitus is considered multifactorial rather than monogenic. Several type 2 diabetes mellitus-susceptibility genes have been identified in the recent GWAS (genome wide association study).

(3) Diabetes mellitus due to specific mechanism and diseases

Unlike the previously described type 2 diabetes mellitus-susceptibility genes, some mutations in a single gene can cause diabetes mellitus (e.g., mitochondrial gene defect). They are classified as one subgroup where "genetic susceptibility to diabetes has been identified by DNA analysis" within this class of diabetes mellitus "due to specific mechanism and diseases"

Secondary diabetes mellitus, e.g., diabetes mellitus associated with a pancreatic or an endocrine disorder, is classified as another subgroup where "diabetes is associated with other pathologic conditions or diseases." Secondary diabetes mellitus may be either caused by decreased insulin secretion or increased insulin resistance.

(4) Gestational diabetes mellitus

The 1999 "Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus" defines gestational diabetes mellitus as diabetes mellitus that develops or is found for the first time during pregnancy. "Reevaluation of Definition, Screening, and Diagnostic Criteria of Gestational Diabetes Mellitus in Japan"[3] recommends the definition to be used until new findings are available. Gestational diabetes mellitus therefore includes (i) previously undocumented diabetes mellitus found in laboratory tests for the first time during the pregnancy, (ii) documented mild glucose metabolism abnormality that develops into diabetes mellitus for the first time during pregnancy and (iii) glucose metabolism abnormality, a milder form of diabetes, that develops for the first time during pregnancy. Postpartum reclassification of gestational diabetes mellitus is recommended.

1) Committee of Japan Diabetes Society for the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee of Japan Diabetes Society on the Classification and Diagnostic Criteria of Diabetes Mellitus. Journal of the Japan Diabetes Society. 42:385-401, 1999

2) Imagawa A. et al. A novel subtype of type 1 diabetes mellitus characterized by a rapid onset and an absence diabetes-related antibodies. N. Engl. J. Med. 342:301-7, 2000

3) Committee on the Definition, Screening, and Reassessment of Diagnostic Criteria of Gestational Diabetes Mellitus in Japan. Reevaluation of Definition, Screening, and Diagnostic Criteria of Gestational Diabetes Mellitus in Japan. Journal of the Japan Diabetes Society. 51:939-947, 2008

3. Epidemiology

The 2007 National Health and Nutrition Survey conducted by the Ministry of Health, Labour and Welfare (MHLW) estimated about 8.9 million people were strongly suspected of having diabetes mellitus and about 13.2 million people were so-called "at-risk group" with whom diabetes mellitus cannot be ruled out,[1] totaling 22.1 million people. Considering that about 7.4 million people were strongly suspected of having diabetes mellitus and about 8.8 million were at-risk group in the 2002 MHLW Diabetes Survey,[2]

the number of current and potential patients with diabetes mellitus has substantially increased. There has also been a rapid increase in the number of patients with diabetes mellitus worldwide, especially in Asia.[3] The alarming trend tells us that this is the century of diabetes mellitus.

According to the data of the Japanese Society for Dialysis Therapy,[4] patients with diabetic nephropathy comprises 34.2% of about 283,000 patients on chronic dialysis and 43.2% (about 16,000 patients) of those who enter chronic dialysis treatment annually in Japan. "The survey on choroidal, retinal and optic nerve atrophy" conducted under the 2005 research supported by Health and Labour Sciences Research Grants for Program to Encourage Research to Overcome Intractable Disease reported diabetic retinopathy was the second major cause of severe visual impairment. Twenty-one percent of Grade 1 visual impairment is caused by diabetic retinopathy.[5] As a risk factor for macrovascular disease (arteriosclerosis), diabetes mellitus is known to increase stroke and coronary artery disease several fold according to a Japanese study.[6]

1) http://www.mhlw.go.jp/houdou/2008/12/h1225-5a.html
2) http://www.mhlw.go.jp/shingi/2004/03/s0318-15.html
3) http://www.eatlas.idf.org/
4) http://docs.jsdt.or.jp/overview/index.html
5) A Research Supported by Health and Labour Sciences Research Grants Outcome Database. The 2005 Intractable Disease Study, Disease and Disability Management 200500858A
6) Oizumi T, Daimon M, Jimbu Y, Wada K, Kameda W, Susa S, Yamaguchi H, Ohnuma H, Tominaga M, Kato T: Impaired glucose tolerance is a risk factor for stroke in a Japanese sample--the Funagata study. Metabolism 57:333-8, 2008

4. Clinical characteristics

Patients with diabetes mellitus may be unaware of their illness and left untreated for long periods because mild metabolic abnormality is hardly symptomatic. Under the condition of metabolic abnormality where moderate or severe hyperglycemia persists, however, symptoms characteristic of diabetes mellitus, such as thirst, polydipsia, polyuria, weight decrease and fatigability, may occur. In most extreme cases acute complications such as ketoacidosis and significant hyperosmolality/hyperglycemia may be followed by disturbance of consciousness and coma, and such patients may die unless they are effectively treated.

Prolonged metabolic abnormality will result in various chronic complications. Specifically, functional and morphological abnormalities of numerous organs such as retina, kidney and nerve will occur. Microangiopathy is a common characteristic of the diabetic complications. If advanced, microangiopathy will result in serious conditions such as visual impairment, visual loss, renal failure and lower extremity gangrene. In many cases the patients with diabetes mellitus are concurrently affected by obesity, hypertension and/or dyslipidemia. Accelerated systemic arteriosclerosis results in macrovascular lesions in the coronary and cerebral arteries, and the arteries in the lower extremities that may cause angina pectoris, myocardial infarction, cerebral infarction, or arteriosclerosis obliterans in the lower extremity. Advanced microvascular complications and arteriosclerotic diseases will significantly deteriorate patient QOL.

III. Efficacy evaluation for OHA

1. Evaluation of symptoms and related measurements

(1) Types and characteristics of symptoms and related measurements

Patients with type 2 diabetes mellitus and mild glucose metabolism abnormality hardly have any symptoms or signs. Hyperglycemic symptoms, e.g., thirst, polydipsia, polyuria, weight decrease and fatigability, occur when the glucose metabolism abnormality advances and the blood glucose increases to ≥ 250 mg/dL, but these symptoms vary between individuals. In patients with much more severe hyperglycemia, dry skin, headache, gastrointestinal symptoms (nausea, vomiting and abdominal pain), decreased blood pressure, tachycardia, convulsion, tremor, consciousness clouding and/or coma may occur. On the other hand, sympathetic symptoms such as perspiration, anxiety, palpitation, tremor finger and pallor may occur when blood glucose decreases to ≤ 70 mg/dL in patients treated with the OHAs such as sulfonylurea (SU), rapid-acting insulin secretagogues or insulin preparations. Further decrease of blood glucose to ≤ 50 mg/dL may cause central nervous symptoms such as consciousness clouding, convulsion, abnormal behavior and coma.

Chronic complications appear as chronic hyperglycemia persists, such as neuropathic symptoms including sensory disturbance in bilateral legs (numbness, pain, loss of sensation and paresthesia), orthostatic hypotension, gastrointestinal symptoms (nausea, vomiting, constipation and diarrhea), erectile dysfunction, dyshidrosis and neuropathic signs including loss of achilles tendon reflex and vibratory sense, and hypoaesthesia. Retinopathic symptoms include floaters and low vision. Nephropathic symptoms include nausea, vomiting, hypertension, edema and dyspnea. Risks of other complications and comorbidity such as stroke, ischemic heart disease, foot gangrene and infection also increase, and related symptoms may occur.

(2) Monitoring of symptoms and related measurements

Patients with mild glucose metabolism abnormality and without advanced complications will have no signs or symptoms. However, body weight and blood glucose should be measured at every patient visit, and funduscopy, Achilles tendon reflex tests and foot examinations should be performed at regular intervals.

Detailed history-taking and physical examinations are important since symptoms associated with severe glucose metabolism abnormality and chronic complications could appear in any part of the body as described in the previous section.

(3) Recommended observations for evaluation of a clinical study

OHA is used to lower the blood glucose to as close to the normal level as possible and prevent onset and progression of complications. Therefore, symptoms and signs associated with severe glucose metabolism abnormality and related complications are not appropriate evaluation markers. The following laboratory tests and other measurements are recommended.

- Glycemic control: The most recommended marker is HbA1c. In addition, glycoalbumin can be a useful short-term glycemic control marker, and 1,5-anhydroglucitol (1,5-AG) can be used for postprandial hyperglycemia assessment in patients with relatively favorable glycemic control.

- Blood glucose: Fasting plasma glucose (FPG) in the early morning is recommended as a stable marker. Postprandial blood glucose should be measured at certain time points (60 minutes, 90 minutes or 120 minutes) after eating the standard meal. In patients with mild glucose metabolism abnormality, 75-g oral glucose tolerance test (75-g OGTT) can be used for evaluation.
- Insulin resistance index: Homeostasis model assessment of insulin resistance (HOMA-R; FPG [mg/dL] x fasting blood insulin [μU/mL]/405) is the most commonly used marker.
- Insulin secretion parameter: Insulinogenic Index (blood insulin (30-minute - 0-minute) [μU/mL]/blood glucose (30-minute - 0-minute) [mg/dL]) in the 75-g OGTT, pre- and post-standard meal blood insulin or blood C-peptide are the most commonly used markers. Measurement of 24-hour urinary C-peptide is also useful.
- Pancreatic β cell functional assessment parameter: While there is no standardized marker, HOMA-β (blood insulin [μU/mL] x 360/fasting blood glucose [mg/dL] - 63), proinsulin/insulin ratio and proinsulin/C-peptide ratio are used.
- Screening items: hematological/blood biochemical/urinalysis, electrocardiogram, etc.
- Physical examination: height, body weight (BMI), blood pressure, abdominal circumference, etc.
- Nephropathy: quantitative urinary microalbumin analysis (urinary albumin/creatinine ratio), urinary protein, renal function indices (e.g., estimated GFR, creatinine clearance), etc.
- Retinopathy: fundus examination by an ophthalmologist
- Neuropathy: Achilles tendon reflex, vibratory sense, etc.
- Arteriosclerosis markers and risk factors: carotid intima media complex thickness (IMT), etc.

Body weight and blood pressure should be measured at every patient visit. HbA1c should be measured every four weeks, and the other glycemic control markers should be measured at appropriate intervals including at baseline and at the end of the treatment.

2. Other precautions

(1) Type 2 diabetes mellitus should be first treated with diet and exercise therapy, and drug therapy is indicated when the target glycemic control cannot be achieved with those alone. Therefore, patients with stable glycemic control who have received diet and exercise therapy need to be selected for appropriate evaluation of the efficacy of an OHA. Uncertain compliance with diet and exercise therapy during the evaluation of an investigational drug may lead to unstable glycemic control and inaccurate evaluation.

(2) Adequate hydration and insulin preparations will be indicated for treatment of patients with severe hyperglycemia. Inclusion of such patients in the evaluation of an OHA will be inappropriate.

(3) The elimination half-life of insulin will be prolonged in patients with severe renal failure. The efficacy of the OHA is therefore likely to be overestimated.

(4) Glucose tolerance may be remarkably decreased in patients with advanced hepatic dysfunction. Accurate efficacy evaluation for an OHA is often difficult in such patients.

(5) Some drugs, e.g., steroids, greatly affect the blood glucose level. Use of such drugs immediately before or during the study may interfere with the efficacy evaluation for the OHA.

(6) In patients with concomitant serious cerebrocardiovascular diseases or proliferative diabetic retinopathy, the conditions may become exacerbated due to sudden decrease of blood glucose after administration of the OHA.

(7) Note that efficacy evaluation may not be possible in patients with abnormal hemoglobin or red blood cell survival when HbA1c is used as the primary endpoint.

IV. Nonclinical studies

Nonclinical studies are required for (1) screening of effective drugs for treatment of target diseases, (2) identification of drug characteristics, (3) evaluation of drug safety in humans, (4) evaluation of drug interactions, and (5) collection of information for appropriately designing clinical studies.

Before using a drug (an investigational drug) in humans for the first time in a clinical trial, the efficacy and safety of the investigational drug need to be estimated based on a thorough evaluation of nonclinical study results. Nonclinical studies should be conducted in an appropriate experimental method according to the guidelines such as "Revision of the ICH Guidelines on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals" (PMSB/ELD Notification No. 1831, December 27, 2000). The following evaluation should be conducted in accordance with the clinical study phase.

1. Origin or history of discovery and usage conditions in foreign countries, etc.

2. Manufacturing process, specifications and testing methods

3. Stability

4. Pharmacology
   (1) Primary pharmacodynamics (*in vitro and in vivo*)

   Standard pharmacological studies of drugs for treating type 2 diabetes mellitus are described below. It should be better to select from the following list to elucidate pharmacological characteristics of the investigational drug. In addition, other appropriate pharmacological studies may be required depending on the mechanism of action of an investigational drug.

   (i) *In vitro* studies to elucidate the mechanism to support the therapeutic benefit

   These studies are carried out prior to animal model studies that support the therapeutic benefit of the investigational drug. The purpose of the study is to screen effective drugs using cells or tissues derived from animals or humans.

   (ii) *In vivo* studies to support the therapeutic benefit

When the investigational drugs are examined in animals, an appropriate animal model should be selected considering the extrapolability to humans. Spontaneously diabetic animal models for evaluation of the therapeutic benefit include *db/db* mouse (type 2, obese), *ob/ob* mouse (type 2, obese), KK-A^y mouse (type 2, obese), GK rat (type 2, non-obese), Zucker fatty rat (obese), ZDF rat (type 2, obese) and Wistar fatty rat (type 2, obese) etc. Otherwise the non-obese rat model induced by streptozotocin during the neonatal period is used as one of the animal models of type 2 diabetes mellitus. The effect of the investigational drugs in single dose study and repeated dose study should be evaluated in more than one of appropriate animal models or normal animals using appropriate pharmacological markers based on the mechanism of action of the investigational drug, such as plasma glucose and plasma insulin level.

(iii) Comparison with established agents

The antihyperglycemic effect shown in the animal model should be compared with established agents. The effects of concomitant therapies with other drugs should also be evaluated as appropriate.

(2) Secondary pharmacodynamic and safety pharmacology studies

(3) Other pharmacology studies

5. Absorption, distribution, metabolism and elimination

6. Acute toxicity, subacute toxicity, chronic toxicity, teratogenicity and other toxicities

V. Clinical studies

The objective of a clinical study is to examine the clinical usefulness of a drug (an investigational drug) based on a comprehensive evaluation of the efficacy and safety in patients. It is necessary to respect human rights as advocated in Declaration of Helsinki and so on because clinical trials are conducted in humans. This is applied to all of the clinical trials for pharmaceuticals. Therefore, clinical trials should be conducted scientifically and properly under the Good Clinical Practice (GCP) to protect safety and respect human rights of participants ethically. Relevant guidelines (see the list at the end) should be referred to as necessary.

Prior to conducting a clinical study, appropriate nonclinical studies in animals (e.g., toxicity studies and safety pharmacological studies) must be completed, and they shall demonstrate the hypoglycemic action of the investigational drug with the acceptable safety in humans. Clinical studies should proceed in a stepwise manner as in other drugs, i.e., from phase I, II and III, in principle. A phase IV study is a post-marketing clinical study or survey. These steps (phases) are not completely separated, and data collected in a phase may lead to the decision-making in the next phase. If any uncertainty about the safety or efficacy arises in a phase, the study needs to go back to the previous phases, including the nonclinical studies, for reevaluation. One should explain to the participants, the pharmacology of the investigational drug, the safety results from the nonclinical and clinical studies up to the time of study planning, the objective of the study and the expected safety measures to be taken in the study. A voluntary written informed consent must also be obtained from each participant.

1. Phase I study

(1) Objective

A phase I study is the first step of a clinical study to use an investigation drug in humans based on the data from nonclinical studies. A limited number of participants (healthy volunteers or, in some cases, patients with type 2 diabetes mellitus) are included in the study, which focuses on evaluation of the safety of the investigational drug in humans. Pharmacokinetic and pharmacodynamic evaluations of the investigational drug are also made in this study phase. One should give the safety of participants top priority when conducting a phase I study. Participants should especially be monitored for occurrence and aggravation of hypoglycemia.

(2) Investigator

An appropriate investigator of a phase I study is a physician with adequate knowledge and experience of clinical pharmacology and evaluation of OHA.

(3) Participants

(i) A phase I study includes healthy adult volunteers. However, the patients with type 2 diabetes mellitus may also be included depending on the characteristics of the investigational drug. Special considerations for a study method will be required if women or elderly people are included in the study.

(ii) Study participants shall be hospitalized or put under a similar condition during the study period.

(4) Study methods

A phase I study should be a double-blind, placebo-controlled study. In principle, the participants are to eat the same standard meal throughout the study period.

(i) Dosage regimen

A single dose study should be conducted, starting with the safe, lowest dose estimated based on the data from the results of nonclinical studies, and carefully titrating the dose. A multiple dose study should follow based on the dose range of which safety and tolerability has been confirmed in the single dose study. Single dose and multiple dose studies may be conducted with different dosage regimens as necessary.

(ii) Observations

Symptoms, signs and laboratory test results should be evaluated in detail at appropriate intervals. Pharmacokinetic evaluation will help understanding the absorption, distribution, metabolism and elimination of the investigational drug and provide useful knowledge to determine appropriate study doses and design. Examples of observations are provided below.

a. Symptoms

b. Signs

Blood pressure, pulse rate/respiratory rate, body temperature, body weight, electrocardiogram, general physical findings, fundoscopy, etc.

c. Laboratory tests

Pharmacokinetics: blood drug concentration, urinary drug concentration

Glucose metabolism: plasma glucose, blood insulin, C-peptide, glucagon, 1,5-AG, glycoalbumin, ketone body, etc.

Hematological tests: white blood cell count, red blood cell count, erythrocyte indices (MCV, MCH, MCHC), hemoglobin, hematocrit, platelet count, leukocyte classification (neutrophil, eosinophil, basophil, monocyte, lymphocyte)

Blood biochemical tests: total protein, albumin, total bilirubin, urea nitrogen, creatinine, uric acid, electrolytes, lipids (total cholesterol, triglyceride, HDL-cholesterol, etc.) AST (GOT), ALT (GPT), ALP, LDH, γ-GTP, CK (CPK) etc.

Urinalysis: appearance (color, cloudiness), specific gravity, qualitative tests (pH, glucose, protein, occult blood, ketone body, bilirubin, urobilinogen), sediment (red blood cell, white blood cell, squamous epithelium, etc.)

Others: laboratory tests required based on results from the nonclinical studies

(5) Evaluation

Category, severity and time of onset of adverse events, treatment required, and types and severity of abnormal variations of laboratory test values should be evaluated on the test results. The pharmacokinetic and pharmacodynamic characteristics of the investigational drug should be analyzed. After the effective dosage regimen of the investigational drug was assessed based on the evaluation, the study may proceed to phase II study.

2. Phase II study

A phase II study starts after the results of the phase I study are thoroughly evaluated in detail. A phase II study is a clinical study in patients with type 2 diabetes mellitus to evaluate the efficacy, safety, and the dosage regimen of the investigational drug as well as the dose-response relationship of the hypoglycemic effect. A phase II study usually consists of an early phase II study to explore the efficacy and safety of the investigational drug in patients and a late phase II study to determine the appropriate dosage regimen to be used in phase III study.

2-1. Early phase II study

(1) Objective

Whether the investigational drug is effective and safe in patients with type 2 diabetes mellitus is examined.

(2) Investigator

An appropriate investigator is a physician who is familiar with the pharmacology of OHA, and who has adequate knowledge and experience of clinical application and evaluation of OHA.

(3) Participants

In principle, a phase II study includes adult patients with type 2 diabetes mellitus with stable conditions and no advanced complications who are not being treated with an OHA or insulin preparations.

(4) Endpoints

HbA1c, FPG, postprandial blood glucose (AUC, 2-hour blood glucose, etc.), 1,5-AG and glycoalbumin are generally used as study endpoints. Appropriate endpoints should be selected based on the characteristics of the investigational drug and the treatment duration. In some cases 75-g OGTT may be used as an endpoint.

(5) Treatment duration

An appropriate observation (run-in) period is required to collect baseline data and start the study treatment in patients with as stable glycemic control as possible. The study duration should be long enough for exploratory evaluation of the efficacy based on the characteristics of the investigational drug and the endpoints (ex. two weeks if the endpoint is the AUC of postprandial blood glucose, one month if it is glycoalbumin and three months if it is HbA1c).

(6) Study design

Ideally, a phase II study should have a randomized, placebo-controlled design. It is important to determine a study dose within the range in which the safety is ensured and the therapeutic benefit of the investigational drug can be expected. In some cases, an established agent may be useful as a reference arm.

(7) Pharmacokinetic exploration

It is useful to measure the blood concentrations of the investigational drug and its metabolites and use the data for evaluation of the pharmacokinetic differences between healthy adult volunteers and patients and the association between the pharmacokinetics and the efficacy of the investigational drug.

(8) Sample size

The sample size should be adequate for exploratory evaluation of the efficacy, safety and dose-response relationship. Adjust the sample size according to the endpoint or the treatment duration.

(9) Observations (example)

a. Symptoms

b. Signs

Blood pressure, pulse rate/respiratory rate, body temperature, body weight, electrocardiogram, general physical findings

c. Laboratory tests

Glucose metabolism: plasma glucose, blood insulin, C-peptide, glucagon, HbA1c, 1,5-AG, glycoalbumin, 75-g OGTT, etc.

Hematological tests: See “1. Phase I study.”

Blood biochemical tests: See “1. Phase I study.”

Urinalysis: See “1. Phase I study.”

d. Others: observations such as compliance with the diet and exercise therapy during the observation (run-in) period, and other particular questions deemed necessary to be addressed from nonclinical and/or phase I studies.

(10) Monitoring intervals

Patients should be monitored at two-week intervals in principle. However, the monitoring interval should be adjusted according to the treatment duration.

(11) Control drug

Using placebo as a control drug will be most reliable and efficient to evaluate the usefulness of the investigational drug in a relatively small-scale, short-term controlled study. When use of placebo is infeasible, a standard drug with established dosage regimen and efficacy may be used as a control drug.

(12) Evaluation

Parameters related to glucose metabolism should be evaluated based on the amount or rate of change. The study may proceed to the next phase after the efficacy and safety are confirmed based on the endpoint evaluation.

2-2. Late phase II study

(1) Objective

A late phase II study determines the appropriate clinical dose and indication.

(2) Investigator

See “2-1. Early phase II study.”

(3) Participants

As with an early phase II study, a late phase II study includes adult patients with type 2 diabetes mellitus with stable conditions who are not being treated with an OHA or insulin preparations.

(4) Endpoints

The primary endpoint should be HbA1c in principle. FPG, postprandial blood glucose (e.g., AUC and 2-hour blood glucose), 1,5-AG and glycoalbumin are also be measured and used as data for determination of a clinical dose. Parameters closely related to glycemic control such as blood insulin, HOMA-R, body weight, serum lipid or adipocytokine may also be used as endpoints as necessary.

(5) Study duration

At least 12 weeks will be required for the study treatment when HbA1c is the primary endpoint. An appropriate duration of observation (run-in) period should also be decided.

(6) Study design

A late phase II study should be a double-blind, randomized controlled study in principle. Since a major change in the diet and exercise therapy may greatly affect the evaluation of the investigational drug, the contents of the diet and exercise therapy as well as patient compliance should be consistent to an extent possible throughout the study period. Ideally, at least three different study doses should be examined.

(7) Pharmacokinetic exploration

See “2-1. Early phase II study.”

(8) Sample size

In principle, the sample size should be adequate to detect a statistically significant difference in the primary endpoint between the investigational drug and placebo. The sample size should also allow for adequate safety evaluation.

(9) Observations

See “2-1. Early phase II study” for the major observations.

(10) Monitoring intervals

Patients should be monitored at four-week intervals in principle, or at two-week intervals if necessary, depending on the treatment duration.

(11) Control drug

Placebo should be used as a control drug in principle. When use of placebo is infeasible, a standard drug with established dosage regimen and efficacy may be used as a control drug.

(12) Evaluation

See “2-1. Early phase II study.”

3. Phase III study

When the investigational drug is highly expected to be a useful pharmaceutical product after the phase II study, a confirmatory study, a phase III study, is conducted. It is important that the usefulness of the investigational drug will be demonstrated in a double-blind controlled study with an appropriate design. A long-term study is also conducted as part of the phase III study to evaluate the safety of the investigational drug and elucidate the type, severity and frequency of possible adverse events and adverse reactions. There are two major types of phase III studies of OHA, studies to evaluate the efficacy and safety in monotherapy, and those to mainly evaluate the safety in concomitant therapies with other OHAs. Since OHA is generally administered for long periods, long-term treatment, specifically, 300 or more patients treated for at least six months and 100 or more patients treated for at least one year, is required in a study in accordance with the ICH E1 guidelines. The drug-drug interaction study to evaluate the effect of the concomitant therapy on the blood concentration is recommended when using the investigational drug concomitantly with a drug with a higher hypoglycemia risk compared with other OHAs (e.g., SU).

3-1. Study for monotherapy

3-1-1. Double-blind, randomized controlled study

(1) Objective

The objective of a phase III study is to evaluate the usefulness of the investigational drug in a more objective manner based on the indication and the dosage regimen determined in the phase II study. Therefore, a double-blind controlled study should be conducted with an appropriate control drug.

(2) Investigator

See “2-1. Early phase II study.”

(3) Participants

As with a phase II study, a study for monotherapy includes adult patients with type 2 diabetes mellitus with stable conditions who are not being treated with an OHA or insulin preparations in principle. Patients who are likely to be treated with the investigational drug in clinical practice after a regulatory approval should be selected.

(4) Endpoints

The primary endpoint should be HbA1c in principle. Other endpoints should be used as necessary based on the results of the phase II study.

(5) Study duration

The adequate treatment duration is required for evaluation of the efficacy and safety of the investigational drug. At least 12 weeks, or ideally 24 weeks, in principle will be required for the study treatment when HbA1c is the primary endpoint. An appropriate follow-up period should also be decided.

(6) Study design

(i) Dosage regimen

The dosage regimen determined in the late phase II study should be used.

(ii) Control drug

An appropriate control drug should be selected from the established agents with established clinical usefulness in Japan at the time of study designing (implementation). However, placebo may be used when no drug is available as an appropriate control based on the characteristics of the investigational drug.

(iii) Sample size

Whether it is a study to demonstrate the superiority of the investigational drug to placebo or a study to demonstrate the noninferiority or superiority of the investigational drug to an established agent, an appropriate sample size should be determined to statistically verify the hypothesis. The sample size should also allow for safety evaluation.

(iv) See “2-2. Late phase II study” for observations, monitoring intervals and evaluation method.

3-1-2. Long-term study

Due to characteristics of OHAs, they are generally administered for long periods. Evaluation of the safety and efficacy of long-term treatment with an OHA is therefore essential. In general, a long-term study is conducted in an open-label manner in parallel with or after a phase III controlled study.

(1) Objective

A long-term study evaluates the safety and efficacy of the investigational drug extensively and for long periods.

(2) Investigator

See “2-1. Early phase II study.”

(3) Participants

See “3-1-1. Double-blind, randomized controlled study.”

(4) Endpoints

The primary endpoint should be the safety of the investigational drug. Efficacy parameters (e.g., HbA1c) should be used as a secondary endpoint.

(5) Study duration

The treatment duration in a long-term study should be at least one year if it is conducted in parallel with a double-blind, randomized controlled study. If a long-term study follows a double-blind, randomized controlled study, the duration should be at least one year in total in both studies.

(6) Study design

(i) Dosage regimen

The same provision in “3-1-1. Double-blind, randomized controlled study” applies in principle. For an investigational drug of which dose is expected to be adjusted during a long-term treatment, the study dose may be adjusted based on predetermined rules.

(ii) Sample size

The sample size should be large enough to allow for safety evaluation of the investigational drug.

(iii) Observations, monitoring intervals, evaluation methods

The same provisions in “2. Phase II study” and “3. Phase III study” apply in principle.

3-2. Long-term study for concomitant therapies (open-label, long-term study for concomitant therapies)

(1) Objective

The objective of a long-term study for concomitant therapies is to evaluate the safety and efficacy of long-term concomitant therapies with the investigational drug and the approved OHAs classified according to pharmacological mechanism of actions. Two-drug concomitant therapies with the investigational drug and the approved OHAs (concomitant therapies expected to be administered to patients in clinical practice) should be evaluated in a single open-label, long-term study for concomitant therapies. Evaluation of all groups of concomitant drugs* that can theoretically be used with the investigational drug and expected to be administered to patients in clinical practice is recommended.

(2) Investigator

See “2-1. Early phase II study.”

(3) Participants

Adult patients with type 2 diabetes mellitus who are inadequately controlled with one of the approved and marketed OHAs administered for a certain period of time should be included in principle.

(4) Endpoints

The primary endpoint should be the safety of the concomitant therapies. Efficacy parameters (e.g., HbA1c) should be used as a secondary endpoint.

(5) Study duration

The duration should be at least one year based on the sample size required by the ICH E1 guidelines for safety evaluation.

(6) Study design

(i) Dosage regimen

For the investigational drug, the same dosage regimen used in the long-term study for monotherapy should be used in principle. For the approved OHA used as a concomitant drug, the usually applied clinical dosage regimen should be used. However, the dosage regimen of the concomitant drug should not be changed during the study period in principle. Certain ethical considerations for patients, e.g., establishing specific criteria for treatment discontinuation, are required.

(ii) Sample size

An adequate sample size is needed for each group of concomitant therapy to allow for safety evaluation (for example, 50 to 100 patients should be included in each group). For concomitant use with drugs with higher hypoglycemia risk compared with other OHAs (e.g., SU), collection of data from 100 patients treated for one year is recommended.

*Groups of concomitant drugs described in this section refer to classification of OHA according to the type of the drug (e.g., SU, biguanide, α-glucosidase inhibitor).

(iii) Observations, monitoring intervals, evaluation methods

The same provisions in "3-1. Study for monotherapy" apply in principle. However, the study design must include thorough precautions against possible hypoglycemia if the concomitant drug (e.g., SU) may induce hypoglycemia in patients.

4. Post-marketing surveillance, etc.

One of the objectives of post-marketing studies and surveillances is to collect information for proper drug use, specifically, information about how the drug is used in patients with a variety of characteristics. The safety, efficacy and usefulness of the drug are to be evaluated based on the extensive post-marketing clinical use. An extensive, long-term clinical experience is especially important because OHA is generally administered to patients for long periods. Information should be collected based on the following points after treatment of longer than one-year. A post-marketing clinical study should be considered if appropriate.

(1) Safety information (e.g., hypoglycemia), information about drug interactions

(2) Effect on diabetic complications
(3) Effect on cardiovascular diseases
(4) Effect on malignant tumor
(5) Efficacy

V. Description of the indication

When an investigational drug is confirmed to be useful in clinical studies conducted based on this guideline, the appropriate description of the indication is “type 2 diabetes mellitus.”

(Supplement)

Supplement (i): Concerning evaluation of cardiovascular risks associated with newly developed OHA

Since cardiovascular risk increases in patients with diabetes mellitus, the US Food and Drug Administration (FDA) has established "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes"[1] (the FDA guidance) to ensure that investigational drugs may not increase the risks. The working team considering the draft of this guideline discussed this point carefully. While comparing Japanese patients with diabetes mellitus with US and European counterparts may not be easy due to the differences in ethnicity and healthcare environment, the estimated annual incidence of cardiovascular diseases in Japanese patients with type 2 diabetes mellitus is about 1% to 1.5%[2-6] and the estimated incidence in the US and Europe is 2% to 2.5%.[7-11] Even though there are differences in patient population studied, e.g., the frequency of patients with history of cardiovascular diseases is higher in US and European studies compared with that among Japanese counterparts, the overall incidence of cardiovascular disease is higher in the US and European diabetes patients. It is of note that scientifically adequate evaluation of cardiovascular risks associated with antidiabetic agents will be extremely difficult, since various other interventions are used in many patients for coexisting conditions. Poor glycemic control lasting for a certain period of time will have a long-term effect on the patient's condition.[12] Undesirable increase of the sample size of the control group for cardiovascular risk assessment may put a large number of patients under poor glycemic control for a significant period, possibly creating ethical issues. Unlike the US and Europe, focusing on cardiovascular risks may not be appropriate considering the epidemiological evidence showing that the leading cause of death among Japanese patients with diabetes mellitus is malignant tumor rather than cardiovascular diseases.[13]

No criterion has been established in Japan for assessment of cardiovascular risks associated with antihypotensive or antilipidemic drugs frequently used in patients with diabetes mellitus, partly because there is reliable evidence that suggests the certain hypotensive and LDL cholesterol lowering effects reduce the cardiovascular risk. Overseas studies of cardiovascular risks for the patients with type 2 diabetes mellitus reported the frequency of cardiovascular events in the patients without history of those events was one-half to one-fourth of that in the patients with the history.[10),11] The FDA guidance therefore recommends clinical studies in the patients with history of cardiovascular events to evaluate the cardiovascular risks associated with anti-type 2 diabetes drugs.[1] In Japan where the prevalence of cardiovascular diseases is lower compared with overseas countries, however, it is not easy to conduct a clinical study in the patients with diabetes mellitus who have a history of cardiovascular complications, that is designed to evaluate the onset of a cardiovascular complication as an endpoint prior to a regulatory approval for the investigational drug. Using a surrogate endpoint in Japanese phase III confirmatory studies may therefore be a realistic alternative.

The meta-analysis of the data from the recent overseas large-scale intervention studies (UKPDS 33 + UKPDS 34, PROactive, ADVANCE, VADT and ACCORD) that evaluated the association between glycemic control and macrovascular risks[14] is worth noting. All the studies included in the meta-analysis were randomized controlled studies (RCT) that examined whether more intensive glycemic control would reduce the so-called hard endpoints such as fatal/non-fatal myocardial infarction, coronary artery disease, fatal/non-fatal stroke and all cause death. Total of 33,040 patients (17,267 received the intensive treatment and 15,773 received the standard treatment). HbA1c decreased from 7.8% at baseline to 6.6% in the intensive treatment group and to 7.5% in the standard treatment group. The difference in amount of change in HbA1c was 0.9%. The meta-analysis neither suggested more strict glycemic control may increase the cardiovascular risks, nor concluded certain drugs or

treatment may increase the risks. However, this report identified lipids, blood pressure, body weight (BMI) and hypoglycemia as possible contributing factors for cardiovascular complications.

Necessity of cardiovascular risk assessment in a long-term clinical study prior to a regulatory approval should be determined in the development of a new investigational drug if any concern arises that is associated with the contributing factors listed above or known cardiovascular risks, if not enough information on these factors is available due to the new mechanism of action of the investigational drug, or if a drug in the same class has been shown to cause cardiovascular complications.

Thus, the cardiovascular effects of new OHA filed for application in Japan should be determined based on the issues specific to diabetes treatment such as hypoglycemia and body weight increase, physiological function tests such as blood pressure and electrocardiogram, laboratory test parameters that may predict the cardiovascular risks such as blood biochemical tests including lipid metabolism markers (e.g., LDL-cholesterol, HDL-cholesterol) as well as the incidence of cardiovascular adverse events.

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Supplement (ii). Concerning combination drugs

Considering that the current drug therapy of diabetes mellitus often involves concomitant therapies, development of the drugs containing two active ingredients with different mechanism of actions of the approved drugs (combination drugs) will proceed in the future. Only appropriate combinations of drugs and doses should be developed based on the pharmacological actions and usage conditions in clinical practice. Evidence to support the significance, efficacy and safety of the combination drug based on nonclinical and clinical studies will be required for filing of application.

(Reference)

Guidelines for clinical studies

http://www.pmda.go.jp/ich/ich_index.html
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International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines

E1: The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions (PAB/ED Notification No. 592; May 24, 1995)

E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (PAB/ED Notification No. 227; March 20, 1995)

E2E: Pharmacovigilance Planning (PFSB/ELD Notification No. 0916001 and PFSB/SD Notification No. 0916001; September 16, 2005)

E3: Structure and Content of Clinical Study Reports (PAB/ED Notification No. 335; May 1, 1996)

E4: Dose-Response Information to Support Drug Registration (PAB/ED Notification No. 494; July 25, 1994)

E5(R1): Handling of Clinical Study Data on Pharmaceuticals Conducted in Foreign Countries (PMSB Notification No. 739; August 11, 1998); Ethnic Factors in the Acceptability of Foreign Clinical Data (PMSB/ELD Notification No. 672; August 11, 1998)

Ethnic Factors in the Acceptability of Foreign Clinical Data: Questions and Answers (Administrative Notice, February 25, 2004)

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E6(R1): Guideline for Good Clinical Practice (MHW Ministerial Ordinance No. 28; March 27, 1997); Enforcement of Good Clinical Practice (PAB Notification No. 430; March 27, 1997)

E7: Studies in Support of Special Populations: Geriatrics (PAB/NDD Notification No. 104; December 2, 1993)

E8: General Consideration for Clinical Trials (PMSB/ELD Notification No. 380; April 21, 1998)

E9: Statistical Principles for Clinical Trials (PMSB/ELD Notification No. 1047; November 30, 1998)

E10: Choice of Control Group and Related Issues in Clinical Trials (PMSB/ELD Notification No. 136; February 27, 2001)

E11: Clinical Investigation of Medicinal Products in the Pediatric Population (PMSB/ELD Notification No. 1334; December 15, 2000)

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E14: The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (PFSB/ELD Notification No. 1023-1; October 23, 2009)
The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Questions and Answers (Administrative Notice; October 23, 2009)

M3(R1): Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (PMSB/ELD Notification No.1019; November 13, 1998)

Revision of Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (PMSB/ELD Notification No.1831; December 27, 2000)

M3(R2): Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (PFSB/ELD Notification No.0219-4; February 19, 2010)

S7A: Safety Pharmacology Studies for Human Pharmaceuticals (PMSB/ELD Notification No.902; June 21, 2001)

S7B: The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (PFSB/ELD Notification No.1023-4; October 23, 2009)

(Others)

Clinical Pharmacokinetic Studies of Pharmaceuticals (PMSB/ELD Notification No. 796; June 1, 2001)

Methods of Drug Interaction studies (PMSB/ELD Notification No. 813; June 4, 2001)

Points to be Considered by the Review Staff Involved in the Evaluation Process of New Drug (April 17, 2008)

Basic Principles on Global Clinical Trials (PFSB/ELD Notification No. 0928010; September 28, 2007)

Clinical Trials based on Genome Pharmacology (PFSB/ELD Notification No. 0930007; September 30, 2008)