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Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus

Draft

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This guideline replaces Note for guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus CPMP/EWP/1080/00.

Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu

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Executive Summary

This guideline intends to address the EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment of patients with diabetes.

1. Introduction (background)

Diabetes mellitus is a metabolic disorder characterised by the presence of hyperglycaemia due to defective insulin secretion, insulin action or both. The chronic hyperglycaemia of diabetes mellitus is associated with significant long term sequelae, particularly damage, dysfunction and failure of various organs – especially the kidney, eye, nerves, heart and blood vessels.

Type 1 diabetes is the result of pancreatic beta cell destruction and is prone to acute complications, such as ketoacidosis. In type 1 diabetes the main goal is optimal blood glucose control to be achieved by optimal insulin replacement therapy, extensive education and disease self management. Prevention of complications and management of pregnancy are important issues.

Type 2 diabetes is a complex disorder which involves various degrees of decreased beta-cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control. Despite combination therapy and/or insulin treatment, a sizeable proportion of patients remain poorly controlled.

Overweight, hypertension and hyperlipidaemia are often associated with diabetes mellitus and multiple cardiovascular risk factor intervention is a key issue in type 2 diabetes. Therefore, global treatment aims in management of diabetes mellitus cover both lowering of blood glucose to near normal levels and correcting metabolic abnormalities and cardiovascular risk factors including weight management. Indeed, it has been shown that normalisation or near normalisation of glucose levels (assessed by changes in HbA1c) in patients with type 1 and type 2 diabetes significantly reduces the risk of microvascular complications (retinopathy, nephropathy and neuropathy); the macrovascular risk reduction in patients with type 2 diabetes is less certain.

In children and adolescents, the diagnosis of diabetes type 1 and type 2 is similar to that in adults; however, the discrimination between them may not always be straightforward. Type 1 diabetes is the predominant form in children. Type 2 diabetes has been recently emerging among – mostly obese - children in puberty and may present with ketoacidosis as the first manifestation of the disease; an obese adolescent with hyperglycaemia may have either type 1 or type 2 diabetes. An important feature of type 2 diabetes in overweight/obese adolescents is the higher insulin resistance and faster beta cell destruction rate relative to adults.

Following may help discriminating between type 1 and type 2 diabetes and monogenic or other genetic non insulin-deficient diabetic forms in children and adolescents:

- Disease definitions and methods of diagnosing defined in international treatment guidelines such as ADA recommendations or those of the International Society for Paediatric and Adolescent Diabetes for the diagnosis of diabetes in children and adolescence are based on presence or absence of obesity,
- family history,
- fasting insulin and C-peptide levels,
- auto-antibodies
- age of onset

2. Scope

This document provides guidance on clinical development programmes intended to support the registration of new medicinal products for the treatment, delay in onset or prevention of diabetes mellitus or preservation of beta-cell function in patients with diabetes.

These notes are intended to assist applicants during the development phase. Any deviation from guidelines should be explained and justified in the Clinical Overview.

Insulin delivery systems (including pumps, autoinjectors, prefilled syringes, etc.) are outside the scope of this document. Biosimilar insulins are covered by the Annex to Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues - Guidance on Similar Medicinal Products containing Recombinant Human Insulin CHMP/32775/05.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83/EC as amended and other pertinent elements outlined in current and future EU and ICH guidelines, especially those on:

- Note for Guidance on Good Clinical Practice - CPMP/ICH/135/95 (ICH E6);
- Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8);
- Studies in Support of Special Populations: Geriatrics - CPMP/ICH/379/99 (ICH E7);
- Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4);
- Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9);
- Choice of the control group in clinical trials - CPMP/ICH/364/96 (ICH E10);
- Requirement on total patient exposure - CPMP/ICH/375/95 (ICH topic E1);
- Ethnic Factors in the Acceptability of Foreign Clinical Data - CPMP/ICH/289/95 (ICH topic E5);
- Guideline on Fixed combination medicinal products - CPMP/EWP/240/95;
- Pharmacokinetic Studies in Man- EudraLex vol. 3C C3A;
- Note for Guidance on the Investigation of Drug Interactions - CPMP/EWP/560/95;
- Clinical investigation of medicinal products in the paediatric population - CPMP/ICH/2711/99 (ICH topic E11);
- Points to Consider on the Need for Reproduction Studies in the Development of Insulin Analogues (CPMP/SWP/2600/01) and on the Non-Clinical Assessment of the Carcinogenic Potential of Human Insulin Analogues - CPMP/SWP/372/01);
- Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005);
- Studies in Support of Special Populations: Geriatric Studies: Questions and Answers - EMA/CHMP/ICH/604661/2009 (ICH E7);
- Evaluation of Medicinal Products for cardiovascular disease prevention - CHMP/EWP/311890/07.

4. Developing and Licensing Glucose Lowering Agents (except insulin products) for the Treatment of Type 2 Diabetes Mellitus

4.1 Specific considerations, strategies and steps in the development.

4.1.1 Pharmacodynamic data

Although there are no specific requirements for pharmacodynamic testing of glucose lowering agents, the mechanism of action of the drug should be evaluated and discussed in relation to that of relevant drugs already available. The pharmacological activity of the main metabolites should be quantified, in diabetic patients when possible (in relevant animal models otherwise), and studied in detail if they are likely to contribute substantially to the therapeutic or toxic effects.

4.1.2 Pharmacokinetics

The pharmacokinetic information required is stated in detail in the appropriate guidelines. Although initial PK studies can be done in healthy volunteers, it is important that PK studies also be performed in all types of patients for whom treatment is intended (including children and elderly). Indeed it may not be assumed that the PK properties observed in healthy subjects will be the same in diabetics and at different age groups. However, factors such as delayed gastric emptying and gastrointestinal transit time or altered renal function can be expected to complicate drug absorption and disposition in a significant number of type 2 diabetic patients. Population PK approach and PK/PD modelling may be additional tools to achieve this objective.

4.1.3 Measures of glycaemic control

The primary purpose of the therapeutic confirmatory studies with the tested agent is to demonstrate a favourable effect on blood glucose control.

4.1.3.1 Glycohaemoglobin (Haemoglobin A_{1C})

Glycohaemoglobin (HbA1C) is the most widely accepted measure of overall, long-term blood glucose control in patients with diabetes. It reflects the mean glucose concentration over the past 2-3 months and thus the immediate clinical consequences of diabetes (hyperglycaemia and its associated symptoms). Moreover, reduction of HbA1C is known to reduce the long-term risk of development of microvascular complications. Therefore, HbA1c is an appropriate primary endpoint to support a claim based on glycaemic control.

The primary analysis of HbA1C should evaluate the difference in evolution from baseline HbA1C between the test compound and the active comparator/placebo. Baseline HbA1C should be included as a covariate in the analysis. The applicant should also justify the clinical relevance of the effect by presenting responder analyses comparing the proportion of patients who reached an absolute value of ≤ 7 and/or 6.5 % across the different treatment groups. Other definitions of a responder should be prospectively identified and justified by the applicant.

A well-validated assay for HbA1C should be used, i.e. reference methods recommended by scientific bodies involved in the international standardisation of HbA1C measurement. Centralised analyses are strongly recommended, at least for therapeutic confirmatory studies.

4.1.3.2 Plasma glucose

Change in fasting plasma glucose (FPG) is an acceptable secondary efficacy endpoint. Changes in average plasma glucose recorded at regular intervals (mean of at least seven measurements, before and after each of three meals and at bedtime; capillary glucose is acceptable, provided that there is confidence in the quality of the glucose measurements) or glucose AUC are also acceptable endpoints. Parameters based on plasma glucose might be used as primary endpoints in short term studies (under 8 weeks), where the use of HbA_{1C} is less appropriate. Serum fructosamine can also be used as an endpoint in short term studies. In addition, a reduction of post-prandial hyperglycaemia, e.g. after a standardized meal, can be used as a secondary endpoint.

The use of devices allowing continuous blood glucose monitoring is encouraged and regarded as useful in adults and children to describe overnight glucose profiles and postprandial hyperglycaemia. Currently these methods still require traditional blood glucose measurements for calibration and it needs to be taken into consideration that glucose measurements from the interstitial fluid lag temporally behind blood glucose values. However, depending on the mode of action and risk for nocturnal hypoglycaemia, continuous blood glucose monitoring may be needed, especially in the paediatric population.

4.1.4 Other measures of metabolic control/status

Improvement of insulin sensitivity and beta cell function are currently not validated as surrogate markers for reduction of micro- and macrovascular complications, but can be assessed as secondary endpoints by using well validated methods.

In insulin-treated type 2 diabetic patients, the entire elimination of the need for insulin in a clinically meaningful proportion of patients, or a relevant reduction in insulin dose accompanied by a clinically significant improvement in the evolution of body weight or reduction in hypoglycaemic events could be considered as a relevant measure of efficacy, in addition to improvement in HbA_{1C}.

The effects of the tested product on serum lipids (LDL and HDL cholesterol, triglycerides) levels should be documented regarding short and long-term effects.

Body weight and other parameters associated with body composition (e.g. waist circumference) should be documented regarding short- and long-term effect.

Long term complications include macrovascular (coronary, cerebrovascular, and peripheral vascular diseases) and microvascular complications (retinopathy, nephropathy, and partly neuropathy). Beneficial effect of the drug on development of these complications can only be evaluated properly in large scale and long term controlled clinical trials.

4.1.5 Associated cardiovascular risk factors

A new glucose-lowering agent should preferably show a neutral or beneficial effect on parameters associated with cardiovascular risk (e.g. body weight, blood pressure, lipid levels).

Before concluding on possible additional benefits or risks, the influence of changes in blood glucose control itself on the changes in the other risk factors should be carefully addressed. For example hypertriglyceridaemia reported commonly in type 2 diabetic patients may improve with good glycaemic control in the majority of patients. Any specific claim regarding improvement of cardiovascular risk factors will require evidence of efficacy over and above the effect of improved glucose control and should be of documented clinical relevance.

4.1.6 Study population and selection of patients

The patients enrolled into clinical trials must be representative of the target population in terms of demography, ethnic background, co-morbidity (especially cardiovascular disease) and type and severity of diabetes. Groups should be sufficiently balanced with respect to age, gender, body mass index, severity and duration of disease. Stratified allocation may be desirable, particularly on the pre-existing metabolic control (e.g. HbA1C ≤8% / >8%) and on pre-study treatment (e.g. diet alone, monotherapy, combination therapy). Studies in specific populations should also be considered (see 4.3 and 5.4).

Monotherapy studies are optimally conducted in patients with early stage of diabetes who have previously failed on diet and exercise. In case patients already treated with glucose lowering agents participate in monotherapy studies, the need for a washout period should be considered (see 4.2.2.1).

Patients enrolled in the trials should be given similar instructions with regard to diet and exercise. To the extent possible, study designs should attempt to simulate clinical practice.

4.1.7 Use of placebo

Placebo-controlled trials are necessary to get relevant information on the glucose-lowering effect of the investigational drug. However, placebo-controlled trials may be viewed as unethical in certain circumstances. Placebo-controlled monotherapy studies of three to six months duration should therefore be reserved for patients at an early stage of the disease (e.g. up to two years after diagnosis). Candidates for these trials should have a relatively low starting HbA_{1C} (e.g. less than 8.5%). Protocols will need to stipulate that patients will have rescue therapy introduced according to a pre-set algorithm if their glucose control consistently deteriorates over a pre-set target (despite reasonable attempts at diet/exercise modification) or be withdrawn from the study. Although the use of strict rescue criteria could be an argument to also allow inclusion of patients with high baseline HbA1c in studies with a duration of more than 3 months, this may lead to a high drop-out rate with subsequent difficulties in interpreting the study results. All patients, including those having received rescue therapy, should be followed up until the end of the study. A reduction in the proportion of patients who are withdrawn due to lack of efficacy compared to placebo according to study protocols may be used to provide additional support for efficacy.

4.2 Methodology of the clinical studies

4.2.1 Therapeutic exploratory studies (dose finding)

The dossier should contain well-designed dose-ranging studies, assessing the lower end of the effective dose range as well as the optimal dose, in order to justify the dosage used in confirmatory clinical trials. Additional information in support of dose selection can also be obtained through modelling and simulation.

A parallel, fixed-dose, double-blind placebo-controlled monotherapy design has proven useful in evaluating new drugs. For therapeutic exploratory studies with a treatment period up to 3 months, a washout period is recommended in patients previously having received glucose lowering agents which are not to be used in the study. If only an add-on claim is requested, dose ranging can be studied as add-on to first line therapy (e.g. metformin). In dose-ranging studies, at least 3 dosages should be studied with a total treatment phase of at least 8 weeks and usually up to 3 months.

FPG should be the primary evaluation criterion in the dose-ranging studies of 8-12 weeks duration. However HbA1C should always be the primary evaluation criterion in the dose-ranging studies of more than 12 weeks duration.

4.2.2 Therapeutic confirmatory studies

Parallel-group, randomised, double-blind, placebo and comparator-controlled studies are necessary. The therapeutic confirmatory trials should aim at demonstrating:

- superiority of the new agent over placebo in at least one monotherapy study of no less than 3 months duration, which could be a dose-ranging study using $HbA1_C$ as the primary endpoint, or the inclusion of a placebo arm for 3 months at the beginning of an active controlled trial (see ICH E10)
- superiority of the new agent over placebo when added to an established background therapy, which represents standard of care in the studied population.
- non-inferiority of the new agent to an established active comparator (in a monotherapy or add-on study depending on the intended indication). At least one active-controlled study should be submitted with the marketing authorisation application.

When predefining a non-inferiority margin, it should be considered that even apparently small reductions in HbA1C have been shown to be clinically relevant in terms of risk reduction of diabetic complications. A margin of 0.3% is generally considered as acceptable. However, the criteria for non-inferiority must be well discussed regarding its clinical relevance in relation to the expected effect on HbA1c. If non-inferiority cannot convincingly be demonstrated, it is necessary to balance the degree of the observed or potential inferiority against some other clinical advantage regarding safety, tolerability, compliance, and/or improvement in cardiovascular risk profile.

Confirmatory studies are typically 6 months in duration but at least one trial, preferably active-controlled, should demonstrate maintenance of effect over at least 12 months.

4.2.2.1 Monotherapy studies

Placebo-controlled monotherapy studies are always required to evaluate the genuine glucose lowering effect and safety profile of the new agent, independent of whether the marketing authorisation is intended for monotherapy or add-on therapy. In addition, a monotherapy study comparing the test drug to metformin is always needed if an indication for first line monotherapy is intended. Even though HbA1c could be acceptable as primary endpoint, other efficacy measures such as effects on micro and macrovascular endpoints would be taken into account before such an indication would be considered approvable.

In any case, approval of a first or a second line monotherapy indication will be a case by case decision taking into account the observed efficacy of the drug in the target population, as well as the size of the safety database and the safety profile.

The study (ies) should include a run-in period, a titration period and a maintenance period.

Run-in (baseline) period

For therapeutic confirmatory studies using HbA1C as the primary endpoint, a washout period is recommended in patients previously having received glucose lowering agents which are not to be used in the study. Subgroup analyses for previously drug- naïve patients and pre-treated patients should be performed.

Titration period

The demonstrated optimal dose should be used for both the test drug and, in active-controlled studies, the comparator. If applicable, the dose should be progressively up-titrated until the maximal tolerated or recommended dose is reached. Uptitration should be performed at 2-4 week intervals unless otherwise justified.

Maintenance period

The overall duration of therapeutic confirmatory active-controlled monotherapy studies should not be less than 6 months, including a maintenance period of at least 16 weeks. For glucose lowering agents with an original mechanism of action, as well as for a marketing authorisation for first line monotherapy, a longer duration may be required. In the maintenance period the dose(s) of the antihyperglycaemic agent(s) (investigational drug, background therapy, comparator) should be kept stable unless a dose reduction is necessary for safety reasons. Dose changes and reasoning should be well documented.

4.2.2.2 Add-on (or combination) studies

These studies aim at determining the efficacy of the investigational drug used as add-on therapy in patients insufficiently controlled with established treatment.

There are many possible therapeutic combinations of glucose lowering agents. The choice of a new combination should be made based on recommendations for diabetes treatment from learned societies (e.g. ADA, EASD, ISPAD) as well as on known contraindications for some combinations. To support the general claim "add on to oral antidiabetic agents" efficacy data would be expected for combinations representing standard of care as well as for combinations for which the additive effect could be expected to be limited (i.e based on mechanisms of action).

For add-on studies, the combination of the new agent and the established agent should be compared to the established agent alone. It is recommended:

(i) to select patients not meeting therapeutic targets on the established agent alone at maximal tolerated or recommended dose. Alternatively, patients could be switched from current therapy (monotherapy or combination therapy not to be tested in the planned study) to monotherapy with the established agent for 8-12 weeks and thereafter to the test combination if therapeutic targets are not met. For these patients groups, analyses of the effects should be made according to previous treatment.

(ii) to select patients with a stable dose of medication during the 8 to 12 weeks preceding the study to ensure that the maximal effect of the previous medication has been achieved and that HbA_{1C} is stabilised at baseline; some products may need longer than 12 weeks to reach their maximal effect.

(iii) to avoid dose adaptation of the concomitant glucose lowering agent(s), unless this is necessary for safety reasons. In the maintenance period the test and concomitant medications should be kept stable as far as possible.

Usually, 16 week duration of the maintenance period is sufficient to demonstrate efficacy in the add-on situation, where a statistically significant and clinically relevant HbA1C reduction should be demonstrated compared to placebo. Improvement in responder rates with the combination in these patients is also desirable. If the HbA1c improvement over placebo is of doubtful clinical relevance, comparison with a commonly used combination is advisable in order to put into perspective the improvement obtained with the new combination.

As stated previously, at least one active controlled trial should be submitted with the marketing authorisation application. If a marketing authorisation for combination therapy is intended, the

active controlled study can be performed in the add-on or in the monotherapy setting (see section "monotherapy studies" above).

Any potential acceptability of an initial (1st line) combination therapy (in drug-naïve patients failing on diet and exercise) will require a scientific consensus on this, as recommended by Learned Societies in the field.

4.2.2.3 Combinations with insulin

Combination therapy of glucose-lowering agents with insulin may occur in different clinical situations and patient populations. Most frequently, insulin therapy is introduced in patients inadequately controlled on other glucose lowering agents. In this case, some or all of the previous agents may be discontinued and insulin is initiated. Less frequently, patients already receiving insulin may benefit from adding another glucose-lowering agent. Reasons for such consideration may be frequent and especially severe hypoglycaemic events preventing the desired level of glycaemic control or insulin-induced weight gain in already obese patients. Overall, the most frequently used combination is insulin plus metformin.

Even though a study in which insulin is added to patients not reaching glycaemic control with the test agent (alone or in combination with metformin) reflects clinical praxis and can provide information concerning the safety of the combination of the test agent and insulin, it is not expected to provide relevant data on the effect of the test drug in this setting. However, relevant safety information from such a study may be useful and reflected in the Product Information.

For an evaluation of both safety and efficacy of the test compound in combination with insulin to support a general claim "combination therapy with insulin", studies should include patients with type 2 diabetes inadequately controlled on a reasonable dose of insulin, e.g. ≥0.5 U/kg/day, as single therapy or in combination with metformin (≥1500mg/day) or both, if stratified. The study population should represent a wide range of BMI and include a substantial percentage of patients with long diabetes duration (e.g. ≥ 10 year) to adequately reflect the whole target population.

After an insulin ± metformin dose-stabilisation period of preferably 8 weeks, eligible patients should be randomized to receiving either the test drug or placebo for at least a total of 26 weeks. Background treatments should generally be kept stable unless dose reductions are necessary for safety reasons (primarily reduction of insulin dose due to hypoglycaemia).

The primary objective of the study should be to demonstrate that the test drug is superior to placebo in HbA1c reduction. Secondary endpoints should, amongst others, include frequency of hypoglycaemia with focus on severe events, change in body weight and in insulin dose.

4.3 Studies in specific populations

Applicants should be encouraged to determine if there are demographic, genetic, metabolic (e.g. C-peptide or other measure of beta-cell function) or other factors which may predict the response to a particular glucose lowering agent. The internal consistency of estimated treatment effects across important subgroups should be investigated. Potential factors should be identified prospectively.

With regards to the characteristics of the trial population it should be considered that a significant number of patients (i.e. at least 30%) should be included from EU countries or countries with lifestyle and diabetes care similar to those of EU member states.

4.3.1 Elderly

Regarding the elderly, it is important to determine whether or not the pharmacokinetic behaviour of the drug in this population is different from that in younger adults. Safety of the tested product, especially occurrence of hypoglycaemia, is a matter of concern in the elderly and very elderly. Therefore, data should be presented for various age groups (65-74; 75-84 and 85+) to assess the consistency of the treatment effect and safety profile in these patients with the non-geriatric patient population. Depending on the data, specific efficacy and safety trials in this population may be needed.

4.3.2 Children and adolescents

The prevalence of type 2 diabetes in children and adolescents is increasing worldwide in parallel with the prevalence of obesity in this population. Due to important potential differences between children/adolescents and adults in several aspects of the disease (i.e. faster decline in beta cell function) and potential safety concerns (based on the mechanism of action of the test product) specific to the paediatric population (e.g. pubertal development, growth, bone development, neurocognitive development) it is in general recommended that separate paediatric trials should be carried out.

4.3.2.1 Age and trial population

Currently, the incidence and prevalence of T2DM is very low in children ≤ 10 years of age. As the mean age of type 2 DM development in children is 13 – 14 years, it is recommended that trials be performed in patients 10 to 18 yr old.

4.3.2.2 Efficacy assessment

In principle the change in HbA1c from baseline to at least 12 weeks versus the control may be acceptable as a primary endpoint, however, the trial duration and endpoint always need to be justified by the type of product (mechanism of action) and trial objective. Completion of an extension phase of 40 weeks is expected before granting a marketing authorization in children unless it can be justified why this is not needed. The type of study (monotherapy or add-on study) should be justified.

It is recommended that all patients should follow a harmonised approach of a structured diet and exercise counselling throughout the trial.

4.3.2.3 Timing of studies

The time of initiation of paediatric studies should follow the ICH E11 guidance. T2DM is considered a serious condition; however, alternative treatments exist. Therefore it is not recommended that studies in children/adolescents are initiated before sufficient safety and efficacy data from adult confirmatory trials are available. If safety concerns exist for a given medicinal product it is not recommended that clinical trials including children are initiated before substantial postmarketing experience in adults is available.

4.4 Safety aspects

4.4.1 General considerations

As for any other medicinal product, the occurrence of blood, liver or skin disorders should be carefully monitored and documented in detail for glucose lowering agents. Regarding liver function, special attention should be paid to elevated activities of liver enzyme, which are observed more frequently in type 2 diabetes. Follow-up should be careful in order to differentiate drug-induced effects on liver function from the spontaneous fluctuations of liver enzyme activities observed in diabetes.

Special efforts should be made to capture potential adverse events that are characteristic of the mechanism of action and the pharmacodynamic properties of the class of products being investigated. This could include possible influence on immune status, tumor inducing effects and infections.

Add-on studies alone do not allow for a definitive assessment of the genuine safety profile of a new compound. Pharmacodynamic interactions almost always occur with other glucose lowering agents, and other effects might occur (e.g. PK interactions, additive toxic effects). It may therefore be difficult to determine the relative contribution of these changes to the observed effect. Therefore, safety data for the test agent in the monotherapy setting are necessary in addition to add-on trials.

4.4.2 Hypoglycaemia

In type 2 diabetes, episodes of severe hypoglycaemia associated with severe CNS dysfunction are rare, but may be of particular concern in children/adolescents and in the elderly and very elderly. A standardised definition of severe and less severe episodes of hypoglycaemia should be established as defined by Learned Societies to include a set of symptoms and a given level of self-monitored blood glucose (see section 7). The likelihood of the diagnosis will be based on the measure of capillary or plasma glucose level at the time of symptoms whenever possible, the description of the symptoms and their evolution following sugar intake, the time of occurrence from last food intake, and the lack of another more likely diagnosis. There should be confidence in the quality of the glucose measurements.

For products associated with hypoglycaemia, a detailed analysis of hypoglycaemic episodes noted in clinical trials should be provided (i.e. analysis stratified for age: ≤ 65 years, > 65 years, >75 years, timing of the episodes in relation to drug exposure, diurnal distribution, and for each episode: time of onset, time after last drug administration, time after meal, severity, duration, outcome of hypoglycaemia, dose of treatment). In addition, nocturnal blood glucose measurements should be considered for such drugs. Use of continuous glucose monitoring, providing more complete information on night profiles, should be considered especially in patient groups at increased risk for hypoglycaemia.

4.4.3 Long-term safety and cardiovascular safety

The target population for glucose lowering agents includes to a large degree patients with co-morbidities and concomitant medications. Different safety aspects should therefore be evaluated in a dataset representative of this population. In addition to an assessment of overall safety data in multiple organ systems, it is essential to, as far as possible, exclude that the new drug increases the risk of macrovascular complications, e.g. cardiovascular disease.

In the past, the assessment of cardiovascular safety in the context of the clinical development of glucose lowering agents has not been possible; the generally benign baseline CV risk profile of

patients recruited in confirmatory studies presented for licensure and the limited treatment or diabetes duration have played a major role. For future developments, it is expected that the development programme provides sufficient information supporting the lack of a drug-induced excess cardiovascular risk.

4.4.3.1 Type of studies

The complete development program will be taken into account in order to detect potential signals that may suggest an increased risk for CV or other rare adverse events. The following general elements should be considered:

- Non-clinical data

Non-clinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects, including CV risk, should be conducted and provided as an instrumental element of the safety evaluation. Animal studies should focus, amongst others, on athero-thrombotic findings, fluid retention, blood pressure, renal function, electrolytes homeostasis, cardiac functionality, repolarisation and conduction abnormalities (pro-arrhythmic effects), etc as outlined in ICH guidelines (e.g. S7A and S7B). If the drug is developed in the paediatric population the guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications should be considered.

- Clinical data

There are two important aspects to consider in terms of detecting signals of adverse events; the overall size of the database and the time needed to detect the signal.

An overall plan for the detection and evaluation of potential adverse events, including justification of the size and duration of the studies with respect to the possibility of detecting safety signals, should be prospectively designed early during the clinical development, optimally by the time of phase II studies. This program should take into consideration key elements of the primary and secondary pharmacology as well as key toxicological findings from non-clinical studies.

Two approaches are conceivable;

- one is metaanalytic approach to safety events. The size of database, as well as the mean duration of the studies, in such cases is expected to be adequate to detect signals for serious and uncommon events, including CV events.
- As an alternate approach or when there is suspicion of an adverse CV signal (from the database), a specific long-term controlled outcome study with at least 18 – 24 months follow-up (depending on the characteristic of a drug and baseline risk of the studied population) would be expected as part of the clinical development program of new glucose lowering agents at the time of submission of the MAA.

With either approach, patients with high risk for cardiovascular events (see further 4.4.3.2), representing a relevant proportion of the diabetic population (according to validated cardiovascular risk scoring systems), are strongly recommended to be included in phase III studies.

The safety evaluation should include a prospective definition of adverse events, particularly cardiovascular safety outcomes of interest that is common for all phase II-III studies, facilitating pooled analysis strategies. Furthermore, applicants should foresee a consistent central adjudication system for all predefined CV and other adverse events of interest during the phase II-III program. Detailed statistical analysis plan for the pooled CV safety data should be prospectively designed.

4.4.3.2 Study Population

In the development program, every effort should be undertaken to include a study population that mimics as much as possible the target population, regardless whether a metaanalytic approach or a specific study approach is used. In either case, an adequate number of high risk patients including those with long duration of the disease (e.g. > 8-10 years), elderly patients, subjects with microvascular disease (e.g. renal dysfunction), subjects with cardiovascular risk factors (e.g hypertension, hyperlipidemia), high risk for cardiovascular complications and confirmed history of ischemic heart disease and/or congestive heart failure should be included in the clinical development. In addition, recognising that conventional CV risk scoring systems may underestimate risk in diabetics, care should be taken to use systems that are applicable to this specific population. [1][2][3]Detailed clinical information allowing a proper characterisation of the baseline characteristics, including ischemic heart disease and congestive heart failure, for patients enrolled in controlled studies must be collected and summarised.

4.4.3.3 Safety outcomes

Concerning CV events, the emphasis will be on major cardiovascular events (MACE) (CV death, non fatal myocardial infarction and stroke) but hospitalisation for unstable angina could also be included in a composite endpoint if the main objective is to exclude a safety signal. It is important to ensure that these are adjudicated events. Other events such as revascularisation and/or worsening of heart failure will also be evaluated.

Additional parameters such as increase in body weight, oedema/ fluid retention and occurrence of hypertension and arrhythmia should be systematically collected. Clinically relevant changes in cardiac function (e.g by echocardiography) should be evaluated if there is an indication of a detrimental effect on cardiac function.

Other safety outcomes should be chosen based on the known safety profile of the product class, the mechanism of action of the investigational drug and/or the non-clinical findings.

Use of relevant terms for coding AEs should be properly defined and homogenised across clinical development, allowing an efficient analysis of safety.

In children/adolescents, at least one year safety data are needed and specific attention should be paid to capture potential adverse effects on growth, bone density, neurobehavioural and sexual maturation. If a specific mechanism of action predicts interference with development then two years safety data in children/adolescents may be needed.

4.4.3.4 Evaluation of the results

For drugs belonging to a well-known class (and mechanism of action) a careful evaluation of the available medical literature together with the absence of pre-clinical and clinical signals of increased cardiovascular risk may lend some support to a meta-analytic approach provided there is no product specific signal from the database. If a benefit or at least absence of harm in terms of CV risk has been shown with the other agents in the class and product specific differences in the off target effects between agents are unlikely this may reduce the need for a specific outcome study.

An integrated safety analysis with specific focus on cardiovascular safety (i.e. with adjudicated pre-determined MACEs) should be submitted at the time of MAA for any drug. A fully powered cardiovascular safety assessment, e.g. based on a dedicated CV outcome study, should be

[1] Ruth L Coleman, Richard J Stevens, Ravi Retnakaran, and Rury R Holman.
Diabetes Care (2007); **30**: 1292-1293.
[2] Score project. European Heart Journal 2003 24(11):987-1003; doi:10.1016/S0195-668X(03)00114-3
[3] Stevens R, Kothari V, Adler AI, Stratten IM, Holman RR.
Clinical Science (2001); **101**: 671-679

submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/ mechanism of action or has emerged from pre-clinical/ clinical registration studies.

Independent on whether a metaanalytic approach or a specific study approach is used, due consideration should be given to the range of analyses presented as in the field of signal detection no single approach to the analysis of data is sufficient to guarantee that relevant signals can be captured.

The overall results of this safety program should be discussed in terms of internal and external validity and clinical justification of the safety outcomes. Acceptability of the data presented will be decided based on its overall quality, the point and interval estimates obtained for the calculation of specific risks, including cardiovascular risk, and the reliability of these estimations. A summary of what is known about CV risk should be proposed for the SmPC.

Indications of increased risk of certain adverse events or unacceptable lack of precision are an important concern and may trigger the request for additional specific long-term outcome trials to exclude an unacceptable increase in CV or other identified risks associated with the new agent.

5. Developing and licensing insulin preparations for the treatment of type 1 and type 2 diabetes mellitus

5.1 Specific considerations

This section provides guidance on new insulin preparations. For biosimilar insulins the reader is referred to the general guidelines on similar biological medicinal products and the specific Annex Guidance on Similar Medicinal Products containing Recombinant Human Insulin. Insulins with a novel route of administration are not within the scope of this guideline. In such cases EMA scientific advice is recommended.

Insulin preparations differ mainly by their kinetic/pharmacodynamic profiles. They are usually classified as short-, rapid-, intermediate-, and long-acting preparations, and are used alone or as free mixtures or premixed preparations of fast/rapid acting insulin and long-acting insulin in various proportions. The same classification is used for insulin analogues, which differ from human insulin preparations by the substitution of amino-acids or other chemical changes, e.g. addition of a fatty acid chain within the insulin molecule.

For novel insulins (e.g. insulin analogues), long term (at least 12-month) efficacy and safety data are essential. For premixed combinations of insulins already individually licensed, pharmacokinetic/ pharmacodynamic data comparing the premixed insulins with the individual components form the basis of the dossier. In case safety data on the free combination are not available or insufficient, clinical data on the fixed combination are needed for safety assessment (e.g. 3-month data).

5.2 Assessment of efficacy

The measures of glycaemic control detailed in the section pertaining to other glucose lowering agents also apply to insulin preparations (see 4.2.2).

However, the rapid changes in plasma glucose levels that occur, particularly in type 1diabetes, call for some specific considerations:

- Both fasting and postprandial blood glucose levels should be measured as secondary endpoints.

- In addition to the evaluation of the overall blood glucose control by HbA_{1C}, at least 7-point capillary-blood glucose profiles (before and after each meal and at bedtime) at regular intervals are necessary, particularly in type 1 diabetic patients.

- Reduction in the amplitude between postprandial hyperglycaemic peaks and fasting blood glucose values in type 1 diabetes is desirable, but will not be accepted as a claim of efficacy unless accompanied by improvement in other measures of blood glucose control such as HbA_{1C}.

Weight gain is frequent in diabetic patients trying to implement intensive glucose control. The evolution of body weight will also be taken into account in the global evaluation of the efficacy and safety, particularly in type 2 diabetic patients.

5.3 Strategy and steps in the development. Methodology of the clinical studies

5.3.1 Pharmacodynamic data

Due to the wide intra- and inter-subject variability in the response to insulin, particularly in type 1 diabetes, pharmacodynamic data are of primary importance for comparison of insulin preparations, including their use in mixtures. Data on the time-action profiles using the euglycaemic clamp technique should be available, providing data based on the glucose infusion rate and the exogenous insulin serum concentrations.

5.3.2 Pharmacokinetics

Although initial PK studies can be done in healthy volunteers, it is required that PK studies also be performed in all types of patients for whom treatment is intended.

For the evaluation of a new insulin or insulin analogue, the comparator drug should be insulin or an analogue with a pharmacological profile similar to the product under consideration. Comprehensive data should be provided on the insulin bioavailability based on peak insulin concentration, time to peak concentration and area under the insulin-time curves. Apart from the kinetic studies in healthy volunteers, studies should be performed in type 1 and in type 2 diabetic patients, adults and children (stratified by age), and in various situations associated with PK variability: insulin dose, site of injection and thickness in fat layer contribute to the rather considerable variation in the PK parameters seen with insulin even in the same individual over time. Age and conditions such as impaired renal or liver function may also contribute to PK variability, particularly with long-acting preparations.

It is recommended to investigate steady-state PK (multiple-dose concentration-time profiles), particularly for long-acting insulin preparations.

It is necessary to show that pharmacokinetic characteristics remain the same if the insulin is used in mixtures. Furthermore, when studying mixtures, fresh mixtures should be tested versus mixtures prepared several hours prior to administration to mimic actual use.

Short/rapid- and long-acting insulin analogues are usually developed for their novel pharmacokinetic properties. Differences in parameters of PK/PD activity should however not be used to claim superiority unless associated with better HbA1c or other statistically significant and clinically relevant benefits e.g. regarding weight or hypoglycaemia.

5.3.3 Methodology of clinical studies

5.3.3.1 Study population and selection of patients

General considerations pertaining to other glucose lowering agents (see 4.1.3) also apply to insulin preparations. Both type 1 and type 2 diabetic patients should be studied. Groups should be balanced with respect to types of insulin regimens. Stratified allocation based on pre-study treatment may also be desirable (e.g. previous insulin preparation, type of insulin regimen). Specific populations should also be considered (see 4.3).

5.3.3.2 Therapeutic exploratory studies

Given the wide intra- and inter-subject variability, crossover designs may be preferable to compare glucose excursions and insulin profiles of different insulin preparations as well as incidence and rate of hypoglycaemia. The study duration should be at least 4 weeks with each insulin preparation for crossover designs, and usually up to 3 months for parallel group designs. In short-term studies, the preferred main end-point is the 24-h blood glucose profile (AUC, Cmax, Cmin).

5.3.3.3 Therapeutic confirmatory studies

General considerations regarding the design of these studies, described in section 4.3.3, also apply here. However the use of a placebo is not ethically justifiable in monotherapy in insulin-dependent diabetic patients. Therefore the active comparator will be an insulin preparation, or an insulin regimen, with a pharmacological profile similar to that of the tested agent.

The use of placebo may be justifiable in the add-on situation in patients with type 2 diabetes, e.g. when studying the effect of a short/rapid-acting insulin given at meal time in combination with longer-acting insulins, or in combination with other glucose lowering agents. Studies should be carried out in patients already treated with long-acting insulin or other glucose lowering agents.

In type 1 diabetic patients, the run-in period should be used to assess the variability in blood glucose profiles and number of hypoglycaemic episodes at baseline. It should be of sufficient duration to allow stabilisation of glycaemic control.

Therapeutic confirmatory studies should assess the safety and efficacy of the insulin preparation in type 1 and type 2 diabetes. The comparative phase should usually be of 6 months in duration. For novel insulin analogues, follow-up data covering a period of at least 12 months should also be available.

For premixed combinations of insulin preparations already individually licensed, controlled trials of shorter duration (i.e. at least 3 months) are usually appropriate and are essentially necessary to assess safety in case safety data on the free combination are not available or insufficient (see section 5.1).

The efficacy and safety of transferring patients from one insulin preparation to another should also be addressed, for example by subgroup analysis based on pre-study therapy.

5.4 Studies in special populations

5.4.1 Elderly

A reasonable number of elderly and very elderly patients (>65 years and >75years, respectively) should be included in the therapeutic confirmatory studies. Particular attention should be paid to the occurrence of hypoglycaemia and optimal dose titration in these patients.

5.4.2 Children

Since type 1 diabetes predominantly develops in children and adolescents, clinical studies for insulin preparations are usually required in the paediatric population, unless otherwise justified. As in the elderly patients, particular attention should be paid to the occurrence of hypoglycaemia and optimal dose titration in these patients. If efficacy and safety of an insulin analogue is demonstrated in adults with type 2 diabetes and in children with type 1 diabetes, additional data in paediatric patients with type 2 diabetes may not be needed.

Paediatric patients should be stratified by age group: < 1 year, 1 to < 6y, 6 to < 12y, 12 to < 18y.

HbA1c is the recommended primary efficacy endpoint (see 4.2.2). Glycaemic variability and hypoglycaemic episodes are important secondary endpoints (see 5.2). Both should be documented, preferably by continuous glucose measurements.

5.5 Safety aspects

5.5.1 Hypoglycaemia

Hypoglycaemia is the biggest obstacle to tight glucose control and is considerably more frequently observed in patients with type 1 diabetes than those with type 2 diabetes. Indicence and rate of both overall and severe hypoglycaemia should be determined in all clinical trials. In order to assess nocturnal hypoglycaemia, the use of continuous glucose monitoring devices should be considered. A relevant reduction of documented episodes of severe hypoglycaemia (see 7.2), if studied in appropriately controlled trials, could itself form the basis for approval of a new treatment, provided that this is not achieved with simply allowing HbA1C to rise.

5.5.2 Local reactions / toxicity

Pain at the injection site and any type of local reaction should be carefully monitored, particularly in patients on long term treatment.

5.5.3 Product immunogenicity / affinity

The antibody status of patients included in long-term trials with new insulin preparations should be monitored, and compared to that observed with existing products. In addition, auto-antibody status and endogenous insulin production should be assessed and reported for all patients entering into clinical trials.

For insulin analogues, comparative data to human insulin should be available on the insulin receptor and IGF1 receptor binding (affinity and dissociation rate), receptor autophosphorylation, phosphorylation of signalling elements, and promotion of mitogenesis (see Points to Consider Document on the Non-Clinical Assessment of the Carcinogenic Potential of Human Insulin Analogues [CPMP/SWP/372/01]).

In case of higher affinity to the IGF-1 receptor of insulin analogues compared to human insulin, it is recommended that fundus photographs are taken during long term trials to detect possible retinal adverse events.

5.5.4 Children

As described for other glucose-lowering agents (see 4.3.2) paediatric studies should preferably be carried out when sufficient safety data in adults are available. Glycaemic variability and susceptibility to hypoglycaemia is higher in children than in adults and is also different among the various paediatric age groups. This is due to higher insulin sensitivity in younger children compared to older children and to adolescents, the latter being largely explained by the "physiological" insulin resistance developing at the time of puberty. In addition, beta cell decline is faster and lifestyle more unpredictable (exercise and food intake) in children compared to adults. Frequent hypoglycaemic as well as hyperglycaemic episodes may impair cognitive development and need to be avoided. Immunogenicity (anti-insulin response) is increased in children compared to adults and should always be evaluated, preferably for a duration of one year including antibody incidence antibody titres.

6. Other potential claims

6.1 Delay in onset / prevention of type 1 diabetes mellitus

The aim of pharmacological interventions in subjects at increased risk for developing type 1 diabetes may be to slow the progression of or to hold the disease in subjects already exhibiting signs of autoimmunogenicity to beta cells or to prevent the disease in subjects not (yet) exhibiting islet related autoantibodies.

Studies have shown that approximately 5% of patients with only one antibody will develop T1DM in the course of 5 years, whereas approximately 50 % of patients with three or more antibodies will develop T1DM after five years. Particularly the combination of GAD and IA-2 autoantibodies may be used efficiently for the prediction of type 1 diabetes in family members of patients with the disease but was also shown to be highly predictive in the general childhood population in Finland. Pharmacological intervention studies that aim to delay or prevent the onset of T1DM should only enrol patients who are at high risk of developing the disease. The validity for the choice of antibodies should be properly justified prior to study start; notably the positive predictive values of such antibodies for development of T1DM should be sufficiently documented.

Clinical studies should be randomized, double blind and placebo-controlled. The primary efficacy endpoint should be the cumulative diabetes incidence. Development or increase of islet related autoantibodies – depending on the status of autoimmunity against beta cells at baseline - could be employed as biomarkers of disease or disease progression to provide additional evidence of efficacy. Immune markers such as anti insulin, anti GAD65, ICA512, and IA-2beta antibodies should be measured at baseline and at predetermined time points during the studies. Genotyping may be important for treatment success.

For safety reasons, a step down approach within the paediatric population is recommended, i.e. commencing studies in younger age groups only if efficacy and particularly relevant safety data are available from older subjects (e.g. 12-<18y, 6-<12 y ; 1-<6 y). In the age group below one year, monogenetic diabetes forms need to be excluded.

Not all subjects at increased risk for developing type 1 diabetes will eventually develop the disease, and if they do it may take many years. Since treatment would likely be given to all patients at risk, including those who would never develop the disease, the safety profile of the preventive measure needs to be rather benign to be acceptable. The clinical relevance i.e. the size and duration of the observed effect, if any, must be carefully balanced against the risks of the intervention.

If the treatment intervention consists of immunosuppressants or immunomodulators, their effects on the general immune responses need to be thoroughly investigated. Endpoints for safety evaluation will depend on the known or suspected mechanism of action of the drug and findings in preclinical and clinical studies. These may include but are not limited to T-cell proliferation in response to conventional antigens, immunoglobulin subclasses, and titres of antibodies in response to primary antigens and recall responses. Considering the experience gained with immune modulating drugs, serious adverse reactions may emerge at a late stage and may include life-threatening infections and malignancies. Therefore, safety follow-up may have to be of substantial duration. Long-term immunosuppressive therapy may only be acceptable in case of outstanding efficacy, if at all.

6.2 Preservation of beta-cell function in patients with new onset type 1 diabetes mellitus

The clinical manifestation of type 1 diabetes represents end-stage insulitis, since only 10-20% of the insulin producing beta cells have been estimated to still be functioning at the time of diagnosis. Nevertheless, patients recently diagnosed with type 1 diabetes and with remaining endogenous insulin reserve may benefit from treatments aiming at preservation of insulin secretory capacity but any pharmacological intervention will need to be initiated as soon as possible after manifestation of the disease to have a chance of showing a meaningful benefit. Attenuating the decline in beta cell function may improve glycaemic control and reduce the risk of hypoglycaemia, at least for a certain time. If the effect is profound and sustained, reduction or delay of diabetic complications may be expected.

Clinical studies aiming at preservation of beta cell function should be randomized, double-blind and placebo-controlled and should include patients with recent onset (e.g. within 3 months) of type 1 diabetes on standard care and a documented residual beta cell function. The primary outcome should preferably consist of co-primary endpoints including not only the change from baseline in C-peptide (e.g. C-peptide AUC) following a physiological stimulus (e.g. liquid mixed meal) under standardized conditions but also HbA1c, frequency of hypoglycaemic episodes, particularly severe events, or the percentage of patients not requiring insulin therapy. Any of these endpoints not included as primary endpoint should be evaluated as important secondary endpoint. Other secondary endpoints should include fasting and postprandial blood glucose concentrations, insulin requirements and frequency of ketoacidosis. The primary endpoint could be measured after 1 year but sustained treatment benefit will need to be shown for a minimum of 2 years after treatment initiation. It is important to choose suitable and highly sensitive assays for reliable C-peptide measurements. It is expected that a clinically meaningful effect on beta cell function will not only lead to relevant improvement in stimulated C-peptide and the chosen co-primary endpoint compared to placebo but is also supported by favourable results on the secondary endpoints.

Again, a step down approach within the paediatric population is recommended (see 6.1). The clinical relevance i.e. the size and duration of the observed effect, if any, must be carefully balanced against the risks of the intervention. For use of immunosuppressants or immunomodulators see section 6.1.

6.3 Delay in onset of type 2 diabetes mellitus

Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), a history of gestational diabetes mellitus, being a first degree relative of a subject with type 2 diabetes, obesity and/or sedentary lifestyle are important known risk factors for developing type 2 diabetes. In addition, the risk for vascular complications has been shown to be increased in subjects with IGT and/or IFG. On the

other hand, there are no conclusive studies to date demonstrating that lowering of fasting or postprandial glucose in subjects with IGT and/or IFG reduces microvascular or macrovascular risk. Mechanistic studies have shown important differences between IGT and IFG populations regarding the pathophysiology of the prediabetic state; IFG is often characterized by reduced hepatic insulin sensitivity, stationary beta cell dysfunction and/or chronic low beta cell mass, whereas IGT is characterized by reduced peripheral insulin sensitivity, near-normal hepatic insulin sensitivity, progressive loss of beta cell function and reduced secretion of glucose-dependent insulinotropic polypeptide.

Lifestyle measures are clearly recommended as first line intervention to improve glycaemia in subjects at high risk for developing type 2 diabetes. However, additional drug therapy may be beneficial in individuals with particularly high risk of developing diabetes, for example, those with worsening glycaemia, cardiovascular disease, or non-alcoholic fatty liver disease when lifestyle interventions are unsuccessful.

Confirmatory studies intended to demonstrate benefit of pharmacotherapy in the delay in onset of type 2 diabetes should include the following considerations.

The study population should consist of subjects who are considered at high risk for developing type 2 diabetes and who do not respond sufficiently to intensive life style interventions. Risk definition and criteria need to be pre-defined using widely accepted tools for diabetes risk assessment. The type and enforcement of appropriate life style interventions should be well documented and (non)response pre-defined. Treatment groups should be balanced for risk factors (such as IFG, IGT, hypertension, hypercholesterolaemia and smoking) known or suspected to convey a different magnitude of risk for progression to type 2 diabetes and for confounding concomitant therapies.

Trials should be randomized, double-blind, placebo-controlled. In addition, appropriate life style interventions (i.e. diet and exercise) should be reinforced in all subjects throughout the study. The treatment phase may vary depending on the mechanism of action of the drug and whether it is intended as short-term or long-term treatment but should always be followed by a wash-out phase which is sufficiently long (e.g. at least 3 months for a glucose-lowering agent) to exclude a masking effect on diabetes. Overall, the studies will likely be of substantial size and duration (years).

Cumulative diabetes incidence or time to diagnosis of diabetes according to established diagnostic criteria is considered an appropriate primary endpoint. However, the effect needs to be statistically significant as well as clinically relevant. Delaying the onset of diabetes may be important but it is currently unclear how much delay would be necessary to convey a reduction of microvascular or macrovascular complications, the real purpose of a pharmacological intervention in ‘at riks’ but ’disease free’ persons. Until further clarification of this issue, the primary endpoint will need to be supported by additional data showing benefit with regard to microvascular and/or macrovascular complications, particularly in case of intended long-term treatment (e.g. ‘early treatment’ with antihyperglycaemic agents). Cardiovascular risk factors such as blood pressure and serum lipids should also be monitored. Assessment of markers/tests of beta-cell function/decline may be included to further support the preventive nature of any observed effect.

Regarding safety, the same considerations as for prevention of type 1 diabetes apply. Not all subjects at risk for developing type 2 diabetes will eventually develop the disease. These subjects would receive treatment without a chance of benefit. Therefore, the safety profile of the preventive measure needs to be rather benign to be acceptable. The clinical relevance of the observed effect, if any, should be discussed and carefully balanced against the risks of the intervention.

7. Definitions

7.1 Diabetes

Diabetes is currently defined (WHO/ADA) as symptoms of diabetes plus:

- Random plasma glucose concentration ≥11.1 mmol/L *[200mg/dl*]

  OR

- Fasting plasma glucose ≥7.0 mmol/L [*126mg/dl*],

  OR

- 2-h plasma glucose concentration after 75 g anhydrous glucose in an oral glucose tolerance test ≥11.1 mmol/L [*200mg/dl*].

  OR

- HbA1c ≥ 6.5%. (The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay, ADA recommendation)

In the absence of symptoms, diabetes should not be diagnosed on a single glucose measurement but needs confirmation.

Impaired glucosetolerance (IGT):

- Fasting plasma glucose concentration <7.0 mmol/l [*126mg/dl*]

  AND

- 2-h plasma glucose concentration ≥ 7.8 and<11.1 mmol/l (140 and 200mg/dl)

Impaired fasting glucose (IFG):

- Fasting plasma glucose 6.1 to 6.9 mmol/l [*110 to 125 mg/dl*]

  AND (if measured)

- 2-h plasma glucose concentration < 7.8 mmol/l (140 mg/dl).

7.2 Hypoglycaemia

The definitions of hypoglycaemia in individual protocols and across protocols within the development program should be standardized. One recommended approach for such standardization is to use classifications of severity from well-accepted sources, such as the ADA:

- **Severe hypoglycemia:**
  An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

- **Documented symptomatic hypoglycemia:**
  An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).

- **Asymptomatic hypoglycemia:**
  An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).

- **Severe hypoglycemia in children:**
  Altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma± convulsions and may require parenteral therapy (glucagon or i.v. glucose).