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

Draft

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

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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 or delay in onset / prevention of diabetes. The current revision refers mainly to an update of the safety section with respect to cardiovascular safety, but also updated guidance concerning e.g. treatment effects on diabetes complications, requirements for first line indications, high strength insulin preparations, definitions of hypoglycaemia and development of oral treatments for patients with type 1 diabetes. In addition, some editorial changes have been implemented.

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 kidneys, eyes, 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 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 dyslipidaemia 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 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 (for differentiating between type 1 and type 2 diabetes in children, see relevant guidelines, e.g. issued by ISPAD).

2. Scope

This document provides guidance on clinical development programmes intended to support the registration of new medicinal products for the treatment of diabetes mellitus. In addition, in section 7 considerations are given for development of products for the delay in onset or prevention of diabetes mellitus or preservation of beta-cell function in patients with diabetes. Experience is however limited and further discussion in case of specific products might be needed.

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 Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMEA/CHMP/BMWP/32775/2005_Rev. 1).

3. Legal basis and relevant guidelines

This guideline should 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) and Guideline for good clinical practice - EMA/CHMP/ICH/135/1995 (ICH E6[R2]);
- Note for Guidance on General Considerations for Clinical Trials - CPMP/ICH/291/95 (ICH E8);
- Note for Guidance on Studies in Support of Special Populations: Geriatrics - CPMP/ICH/379/95 and Questions and Answers - EMA/CHMP/ICH/604661/2009 (ICH E7);
- Note for Guidance on Dose Response Information to Support Drug Registration - CPMP/ICH/378/95 (ICH E4);
- Note for Guidance on Statistical Principles for Clinical Trials - CPMP/ICH/363/96 (ICH E9);
- Note for Guidance on Choice of the control group in clinical trials - CPMP/ICH/364/96 (ICH E10);
- Note for Guidance on Population Exposure - CPMP/ICH/375/95 (ICH E1);
- Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data - and Questions and Answers - CPMP/ICH/289/95 (ICH E5);
- Guideline on clinical development of fixed combination medicinal products - EMA/CHMP/158268/2017;
- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population - CPMP/ICH/2711/99 (ICH E11);
- Points to consider on the need for assessment of reproductive toxicity of human insulin analogues - CPMP/SWP/2600/01 Final, 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;
- Guideline on the evaluation of medicinal products for cardiovascular disease prevention - CHMP/EWP/311890/2007;
- Guideline on immunogenicity assessment of therapeutic proteins - EMEA/CHMP/BMWP/14327/2006/Rev.1.
- Reflection Paper on assessment of cardiovascular safety profile of medicinal products - EMA/CHMP/50549/2015;
- Risk minimisation strategy for high strength and fixed combination insulin products - Addendum to the good practice guide on risk minimisation and prevention of medication errors - EMA/686009/2014;

4. Developing and licensing glucose lowering agents (except insulin products) for the treatment of type 2 diabetes mellitus

4.1. Patient selection

The patients enrolled into clinical trials must be representative of the target population in terms of demography, ethnic background, co-morbidities (including cardiovascular disease) and type, duration and severity of diabetes. Ideally, treatment groups should be sufficiently balanced with respect to age, gender, body mass index, severity and duration of disease. Randomisation should result in a balance across most factors but stratified allocation may be desirable, particularly regarding pre-existing metabolic control (e.g. HbA1c ≤8% vs. >8% [≤64 vs. >64 mmol/mol]) and pre-study treatment (e.g. diet alone, monotherapy, combination therapy). Studies in specific populations should also be considered (see 4. 5).

Monotherapy studies are optimally conducted in patients with early stage of diabetes who have previously failed to achieve glycaemic control on diet and exercise or have had a short treatment course with glucose lowering agents.

Patients enrolled in the trials should be given similar instructions with regard to diet and exercise.

4.2. Assessment of efficacy

4.2.1. Efficacy criteria / Treatment goals

Treatment of patients with type 2 diabetes should be based on a holistic approach in order to improve blood glucose levels and reduce the risk of both micro- and macrovascular complications. Even though the primary aim of the confirmatory studies with the glucose lowering agent is to demonstrate a favourable effect on blood glucose control, it is also important to consider effects of the test agent on other CV risk factors.

It is important to be precise with respect to the trial objectives. In particular, intercurrent events will occur which may either preclude observations of the variable of interest or affect its interpretation. For example, a certain proportion of patients will not adhere to randomised treatment (e.g. due to intolerance, lack of efficacy), require rescue medication or a change of background medication. It is important to consider these events prospectively and to address them when defining a treatment effect of interest. Specification of strategies to address these intercurrent events to precisely define a treatment effect of interest should then, in turn, inform trial design, data collection and choice of analysis method.

4.2.2. Measures of glycaemic control

4.2.2.1. Haemoglobin A1c

Glycated haemoglobin (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. 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 target of estimation should estimate a treatment effect based on the difference in HbA1c from baseline to the end-of-trial (or other predefined time for assessment of the effect) between the

test compound and a control treatment. The actual adherence to treatment should be reflected in the target of estimation. Specifically, since patients are not expected to benefit once treatment is discontinued (e.g. due to adverse events) the treatment effect should be estimated based on observed or modelled data reflecting adherence to treatment as observed in the clinical trial.

Other important intercurrent events to consider are the changes to, or introduction of, other medication that will influence HbA1c values, including use of protocol-defined rescue medication. The impact of additional medication complicates the evaluation of the effect of the test product compared to placebo or active control. Therefore, the treatment effect can be estimated under the assumption that rescue medication, or use of other medications that will influence HbA1c values, was not introduced (hypothetical scenario), provided that a reliable estimate of that effect can be obtained.

The analytical approach, including the handling of missing data, should be aligned to the agreed target of estimation. Data obtained after discontinuation of treatment are of principle interest for the estimand described above, but since data obtained after initiation of rescue medication are not (they reflect the effect of the additional or rescue medication itself), statistical modelling would be required. Modelling based on data obtained in the placebo group might be an acceptable approach to reflect discontinuation from treatment and a scenario in which additional medication was not introduced.

For active controlled trials with a non-inferiority hypothesis the same primary estimand might be adopted, but additional approaches should be specified to address the impact of important protocol violations and deviations.

Other approaches with respect to evaluations of the treatment effect should be justified.

The clinical relevance of the observed effect should be further justified by analysing the difference in proportion of patients who reached an absolute HbA1c value of ≤ 7 and/or 6.5 % (≤ 53 and/or 48 mmol/mol) at end-of-trial without the use of additional medication and who remain adherent to treatment. Such analyses may also provide guidance on how many patients might tolerate the investigational drug and benefit from treatment in the long term.

Other definitions of a responder should be prospectively identified and justified by the applicant.

Combined endpoints e.g. reflecting the percentage of patients achieving target HbA1c without hypoglycaemia can be informative as secondary endpoints in some situations but should be pre-specified.

4.2.2.2. 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) or glucose AUC are also acceptable endpoints. Nocturnal hypoglycaemia may also be a relevant endpoint. Strategies to handle intercurrent events when estimating the effect of treatment on these variables can be the same as for haemoglobin A1c.

Depending on the mode of action of the test agent and risk for hypoglycaemia of the study population, particularly nocturnal hypoglycaemia, continuous blood glucose monitoring should be considered to provide additional relevant information.

Parameters based on plasma glucose might be used as primary endpoints in short term studies (under 8 weeks), where the use of HbA1c 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.

In confirmatory studies, plasma glucose is often used to define cut offs for glycaemic rescue criteria. A reduction in the proportion of patients who have received rescue therapy and/or are withdrawn due to lack of efficacy compared to placebo according to study protocols may be used to provide support for efficacy.

4.2.2.3. Insulin parameters

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.

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 meaningful 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 or maintenance of HbA1c. Patients with a meaningful increase in concomitant treatment or use of rescue medication would be classified as non-responders.

4.2.3. Other cardiovascular risk factors

Short- and long-term effects of the tested product on serum lipids (LDL and HDL cholesterol, triglycerides), body weight and other parameters associated with body composition (e.g. waist circumference) as well as blood pressure and heart rate should be documented.

A new glucose-lowering agent should preferably show a neutral or beneficial effect on such parameters associated with cardiovascular risk. Before concluding on possible additional benefits with respect to changes in cardiovascular risk factors, the influence of changes in blood glucose control itself 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.

4.2.4. Effect on long term complications

Long term complications include macrovascular (coronary, cerebrovascular, and peripheral vascular diseases) and microvascular complications (retinopathy, nephropathy, and neuropathy). Beneficial effects of the drug on development of these complications in the intended target population can only be evaluated properly in large scale and long term controlled clinical trials and are not a mandatory requirement for the approval of a new medicinal product but may be needed for a first line unrestricted monotherapy indication (see 4.4.4.).

If beneficial effects on micro and/or macrovascular complications have been documented in (parts of) the target population, such data may be included in the product information (SmPC section 5.1). This would reflect that the treatment, in addition to improving glycaemic control, also has a documented effect on long term complications, both being part of the concept of ” treatment of diabetes”.

4.2.5. Patient-reported outcomes

The use of disease-specific patient-reported outcomes for diabetes is recommended as it may reveal important information on how a treatment affects quality-of-life. Furthermore, such information will help to contextualize observed effects on measures derived from continuous glucose monitoring such as glucose variability, glucose excursions and time spent in normal range.

4.3. Methods to assess efficacy

4.3.1. Glycaemic control

4.3.1.1. Haemoglobin A1c

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.

4.3.1.2. Plasma glucose

For recording of plasma glucose, capillary glucose is acceptable provided that there is confidence in the quality of the glucose measurements. However, 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.

4.3.1.3. Insulin sensitivity/Beta cell function

Insulin sensitivity and beta cell function should be assessed by using validated methods as justified by the Applicant.

4.3.2. Patient-reported outcomes

The inclusion of patient-reported outcomes to assess the treatment burden and impact on daily life, diabetes management, compliance and cognition is recommended. In this case it is important that the questionnaires or scales are validated for use in the setting of diabetes.

4.4. Study Design

4.4.1. 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). It should be taken into consideration that 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 obtain relevant information.

4.4.2. Pharmacodynamics

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. If there are pharmacologically active metabolites, the contribution to therapeutic and/or toxic effects should be discussed.

4.4.3. Exploratory and dose finding studies

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(s) 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 is recommended for 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 intended, 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 dose-ranging studies of 8-12 weeks duration. Serum fructosamine can also be used as an endpoint in short term studies. However HbA1c should always be the primary evaluation criterion in dose-ranging studies of ≥12 weeks duration.

4.4.4. Confirmatory studies

4.4.4.1. General design elements

Parallel-group, randomised, double-blind (whenever feasible), placebo and active-comparator-controlled studies are recommended. 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, phase II study using HbA1c 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)

and

- Superiority of the new agent over placebo when added to an established background therapy, which represents standard of care in the studied population

and

- Non-inferiority of the new agent to an established active comparator (in a monotherapy or add-on study depending on the intended indication) representing standard of care. At least one active-controlled study is recommended to be submitted with the marketing authorisation application.

Confirmatory studies (except for placebo controlled monotherapy 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. The primary endpoint should be HbA1c while secondary endpoints should include other measures of glycaemic control as well as the effect on other cardiovascular risk factors (see section 4.2).

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. While a margin of 0.3% (3 mmol/mol) is generally considered as acceptable, the choice of the margin should always be discussed in the clinical context. Other factors to consider are the expected benefit over placebo for the active comparator and the details of the trial design. 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 e.g. safety, tolerability, compliance, and/or improvement in cardiovascular risk 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 although in case of studies with duration> 3 months, a wash out period may not be needed. 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

In the maintenance period the dose(s) of the glucose lowering agent(s) (investigational drug, background therapy, comparator) should be kept stable unless a dose adaption is necessary for safety reasons (e.g. hypoglycaemia). Dose changes and reasoning should be well documented.

4.4.4.2. Monotherapy studies

Comparison of the test agent to placebo in the monotherapy setting is 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. Placebo-controlled monotherapy studies of more than three months in duration should be reserved for patients at an early stage of the disease (e.g. up to two years after diagnosis). Use of placebo for more than 6 months is generally not recommended. Candidates for these trials should preferably have a relatively low starting HbA1c (e.g. less than 8.5% [69 mmol/mol]). Protocols will need to stipulate that patients have rescue therapy introduced according to a pre-defined algorithm if their glucose control consistently deteriorates over a pre-set target or be withdrawn from the study. Although the use of strict glycaemic 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.

If an indication for first line (unrestricted) monotherapy is intended, a monotherapy study comparing the test drug to metformin is usually needed, unless the robustness and magnitude of the glucose lowering effect of the test drug is very convincing. In addition, beneficial effects on micro and/or macrovascular endpoints and a well characterized safety profile (including data on long term safety) should be documented before a first line monotherapy indication would be considered approvable.

4.4.4.3. 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 other glucose lowering agents” efficacy data would be expected for combinations representing standard of care. In addition, combinations for which specific safety issues (e.g. hypoglycaemia) are expected (i.e. based on mechanisms of action) should be investigated. Study results from all combination studies will be reflected in the product information.

Add-on studies should be placebo- or active controlled. 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 (background therapy) for 8-12 weeks and thereafter, if therapeutic targets are not met, should be randomized to receive the test agent or placebo/active control as add-on. For these patient groups, analyses should be stratified 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 HbA1c is stabilised at baseline; some products may need longer than 12 weeks to reach their maximal effect.

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

4.4.4.4. 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 initiated in patients not reaching glycaemic control with the test agent (alone or in combination with another glucose-lowering agent, most likely metformin) would reflect the most common clinical scenario, it is not expected to provide relevant data on the effect of the test drug in this setting. However, relevant safety information on the combined use of the test agent and insulin may be gained from such a study and may be reflected in the Product Information.

For appropriate evaluation of both safety and efficacy of the test compound in combination with insulin, the test agent should be added in patients with type 2 diabetes inadequately controlled on a reasonable dose of insulin as single therapy or in combination with another glucose-lowering agent, typically metformin or both, if stratified. Treatment groups should be balanced with respect to insulin regimens (e.g. basal only vs. basal-bolus regimen). In order to support a general claim “combination therapy with insulin”, 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) and elderly patients 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). Rescue criteria should be predefined to ensure that patients will not sustain prolonged periods of poor glycaemic control.

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 and may also include the percentage of patients achieving target HbA1c without hypoglycaemia.

Other study designs are principally possible. In such cases EMA scientific advice is recommended.

4.5. Studies in special 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. Those potential factors should ideally be identified prospectively. Even if no heterogeneity is expected, the internal consistency of estimated treatment effects across important subgroups should be investigated

With regards to the characteristics of the trial population it should be considered that a relevant number of patients should be included from EU countries or countries with lifestyle and diabetes care similar to those of EU member states.

4.5.1. 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+ years) 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.

4.5.2. 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.

Age and trial population

Currently, the incidence and prevalence of type 2 diabetes 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 less than 18 years old.

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 (see also section 4.2 concerning definition of the scientific question of interest). Completion of an extension phase to provide a total of at least 12 months of exposure 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.

Timing of studies

The time of initiation of paediatric studies should follow the ICH E11 guidance. Type 2 diabetes 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 trials are available. If significant safety concerns exist for a given medicinal product it is not recommended that clinical trials including children are initiated before post marketing experience in adults is available.

4.6. Safety aspects

4.6.1. General considerations

As for any other medicinal product, the occurrence of e.g. 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 enzymes, 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, tumour-inducing effects and infections/inflammations (e.g. pancreatitis).

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 important in addition to add-on trials.

4.6.2. 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. A standardised definition of severe and less severe episodes of hypoglycaemia should be used as defined by Learned Societies to include a set of symptoms and a given level of self-monitored blood glucose (see also sections 5.6.1 and 8.2). Hypoglycaemia should be confirmed by measuring capillary or plasma glucose levels whenever possible. There should be confidence in the quality of the glucose measurements.

A detailed analysis of hypoglycaemic episodes noted in clinical trials should be provided (e.g. 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 drugs with a propensity to cause hypoglycaemia. Use of continuous glucose monitoring, providing more complete information on night profiles, should be considered for certain products and patient groups at increased risk for hypoglycaemia.

4.6.3. Cardiovascular safety

It is expected that the drug development program, containing all relevant clinical and non-clinical data, adequately characterizes the cardiovascular safety profile enabling an evaluation of the cardiovascular safety in the marketing authorization application. This refers in particular to products with a new mechanism of action or products belonging to a drug class for which the cardiovascular safety profile is not yet established or questioned, e.g. in case of a detrimental effect on another cardiovascular risk factor.

Requirements for the evaluation and quantification of the cardiovascular risk at the time of licensing are further outlined in the CHMP's "Reflection paper on assessment of cardiovascular safety profile of medicinal products" (EMA/CHMP/50549/2015).

4.6.4. Immunogenicity

If the new glucose-lowering agent is a protein, development of anti-drug antibodies should be monitored including antibody incidence and titres over time. Regarding general aspects on immunogenicity assessment, reference is made to the "Guideline on immunogenicity assessment of therapeutic proteins" (EMEA/CHMP/BMWP/14327/2006/Rev.1).

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 "Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues" (CHMP/32775/2005_Rev.1). 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 rapid-, short-, intermediate-, and long-acting preparations, and are used alone or as free mixtures or premixed preparations of rapid/short-acting insulin and intermediate/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. Patient selection

5.2.1. Study population and selection of patients

General considerations pertaining to other glucose lowering agents (see section 4.1) also apply to insulin preparations. Both type 1 and type 2 diabetic patients should be studied. Randomisation should

result in a balance across most factors in the study groups but stratified allocation may be helpful e.g. with respect to types of previous insulin regimens. Specific populations should be considered (see section 4.5).

5.3. Assessment of efficacy

5.3.1. Efficacy criteria / Treatment goals / Methods to assess efficacy

The measures of glycaemic control detailed in the section pertaining to other glucose lowering agents also apply to insulin preparations (see also section 4.2 concerning definition of the scientific question of interest).

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 HbA1c, at least 7-point capillary-blood glucose profiles (before and after each meal, at bedtime and during the night) at regular intervals are necessary, particularly in type 1 diabetic patients. Alternatively, continuous glucose monitoring could be considered, particularly in paediatric patients.
- Reduction in the amplitude between postprandial hyperglycaemic peaks and fasting blood glucose values is desirable, but will not be accepted as a claim of superiority of a new insulin compared to an established insulin, unless accompanied by a relevant improvement in blood glucose control (measured by HbA1c), hypoglycaemia or other clinically meaningful outcomes.

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.

5.4. Study design

5.4.1. 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. Population PK approach and PK/PD modelling may be additional tools to achieve this objective.

For the evaluation of a new insulin, the comparator drug should be an established insulin with a pharmacological profile similar to that of the product under development. Comprehensive pharmacokinetic data should be provided including peak insulin concentration, time to peak concentration, area under the insulin-time curve and half-life. 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. 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.

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

5.4.2. Pharmacodynamics

Pharmacodynamic data in insulin-sensitive patients with type 1 diabetes are of primary importance for the comparison of insulin preparations, including their use in mixtures. The glucose clamp technique is the preferred method to assess the time-action profile of insulins.

5.4.3. Therapeutic exploratory studies

In order to reduce 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. The cross-over design is not recommended for long-term trials because of expected carry-over effects due to improvement in metabolic control. In short-term studies, the preferred main end-point is the 24-h blood glucose profile (AUC, Cmax, Cmin).

5.4.4. Therapeutic confirmatory studies

General considerations regarding the design of confirmatory studies, described in section 4.4.4, also apply here. However the use of a placebo is usually not ethical in insulin-dependent diabetic patients. Therefore, studies will generally be active-controlled using an insulin preparation as comparator with a pharmacological profile similar to that of the tested agent.

In patients with type 1 diabetes, 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. Patients should be treated to glycaemic target taking into account limiting adverse effects, particularly hypoglycaemia. 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.

5.5. Studies in special populations

5.5.1. Elderly

A reasonable number of elderly patients (65-74; 75-84 and 85+ years) 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.

5.5.2. Children

Since type 1 diabetes predominantly develops in children and adolescents, clinical studies for insulin preparations are normally 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. However, as described for other glucose-lowering agents (see section 4.3.2) paediatric studies using a novel insulin should preferably be carried out when sufficient safety data in adults are available. If efficacy and safety of a novel insulin 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 (i.e. extrapolation may be possible).

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. Glycaemic variability and hypoglycaemic episodes are important secondary endpoints (see section 5.3). Both should be documented, preferably by continuous glucose measurements.

5.6. Safety aspects

5.6.1. 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. Incidence and rate of both overall and severe hypoglycaemia should be determined in all clinical trials. It is recognized that glycaemic thresholds for responses to hypoglycaemia vary among individuals with diabetes as well as in the same individual with diabetes as a function of their HbA1c levels and hypoglycaemic experience. However, in the context of drug development, it is of importance to identify and record a level of hypoglycaemia that needs to be avoided because of its immediate and long-term danger to the individual(see section 8.2).

In order to assess glucose variability and nocturnal hypoglycaemia, the use of continuous glucose monitoring devices should be considered. A relevant reduction of documented episodes of hypoglycaemia, particularly severe events, if studied in appropriately controlled trials, could support a claim of superiority over the insulin used a s comparator provided that this is not achieved with simply allowing HbA1c to rise.

5.6.2. 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.

5.6.3. Product immunogenicity / affinity

Immunogenicity of new insulin preparations should be assessed by determining antibody incidence and titres over time, and should be compared to that observed with established insulin products. For novel insulins, one-year immunogenicity data are usually required pre-licensing. Regarding general aspects on immunogenicity assessment, reference is made to the Guideline on immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006/Rev.1).

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.

5.6.4. High strength and fixed combination insulin products

For high strength insulins (i.e. higher than EU-wide standard of 100 units/ml concentration) and fixed combination of insulin with another non-insulin injectable glucose-lowering agent, concerns about potential medication errors should be taken into account.

The high strength insulin or the fixed combination insulin product should preferably be manufactured in pre-filled pens only. The pre-filled pen should automatically adjusts for strength and no dose conversion or re-calculation should be required when switching between standard strength (100 units/ml) and higher strength or fixed combination insulin products within the same product range.

For products where insulin is combined with another injectable glucose-lowering agent in a prefilled pen, the number of 'dose steps' should always be equivalent to the number of units of insulin to be administered, i.e. the dose counter window on the pen will display the number of dose steps and this will be the same as the number of units of insulin.

5.6.5. Children

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 (physical activity and food intake) in children compared to adults. Frequent hypoglycaemic as well as hyperglycaemic episodes may impair cognitive development and should 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 and antibody titres.

6. Non-insulin medicinal products for the treatment of type 1 diabetes

Insulin therapy is always required for the treatment of type 1 diabetes. However, the possibility of achieving glycaemic goals can be hampered by the risk of severe hypoglycaemia. New therapies that,

in addition to insulin, may improve glycaemic control and/or reduce the risk of hypoglycaemia are being developed.

In order to confirm such benefits, phase III studies should be placebo controlled and an initial run-in phase with the aim to optimize the insulin treatment is recommended. The preferred primary superiority endpoint should be the change from baseline HbA1c after approximately 26 weeks of double-blind treatment (see also section 4.2 concerning definition of the scientific question of interest). To show durability of the effect, a 6 month extension phase is required. Insulin doses should be adjustable during the study. It is also necessary to demonstrate that HbA1c decrease does not come at the cost of unacceptably increased hypoglycaemia risk.

Alternatively, if non-inferiority testing of Hb1Ac vs. placebo on top of freely titrated insulin is the primary endpoint, incidence and/or rate of hypoglycaemia should be a co-primary endpoint.

Defining a composite endpoint encompassing HbA1c decrease and risk of hypoglycaemia (e.g. “HbA1c <7% without documented symptomatic hypoglycaemia” or “HbA1c <7% without nocturnal or severe hypoglycaemia”) could be included as a secondary endpoint.

Reduction in insulin need alone is not regarded as a relevant endpoint. It has to be demonstrated that this is accompanied by clinically relevant changes such as reduced incidence of hypoglycaemia or reduced body weight gain; however, the latter may be less relevant in patients with type 1 diabetes when they are lean and have a low degree of insulin resistance. Further, a reduction in insulin dose in insulin deficient patients could increase the risk of ketoacidosis. Therefore, the risk of diabetic ketoacidosis should be closely followed during the studies.

7. Other potential claims

Considering the limited experience with studies in the areas of diabetes prevention and preservation of beta-cell function and absence of licensed medicinal products for these indications, only high-level advice can be given.

7.1. 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 autoimmunity to beta cells (secondary prevention) or to prevent the disease in subjects not (yet) exhibiting beta cell autoantibodies (primary prevention). So far, pharmacological interventions have only been tested in the secondary prevention setting.

Studies suggest that approximately 5% of subjects with only one autoantibody and approximately 50 % of subjects with three or more autoantibodies will develop type 1 diabetes in the course of five years. Within the group of at-risk subjects with beta cell specific autoantibodies, there are subgroups with even higher risk which can be identified based on insulin secretion and glucose tolerance.

Unless the test agent has an absolutely benign safety profile, pharmacological intervention studies that aim to delay or prevent the onset of type 1 diabetes should only enrol patients who are at high risk of developing the disease. The validity for the choice of antibodies and other criteria should be properly justified prior to study start; notably the positive predictive values of such antibodies for development of type 1 diabetes should be sufficiently documented.

Clinical studies should be randomized, preferably double blind and placebo-controlled. The primary efficacy endpoint should be the cumulative diabetes incidence. Development or increase of beta cell specific 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. Observations such as reversal of dysglycaemia, improvement in glucose tolerance or preservation of beta cell mass would also support efficacy. 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, monogenic 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, 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 immunosuppressive agents, 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.

7.2. Preservation of beta-cell function in patients with type 1 diabetes mellitus

The clinical manifestation of type 1 diabetes is thought to represent end-stage insulitis, since only 10-20% of the insulin producing beta cells have been estimated to be still functioning at the time of diagnosis. Nevertheless, patients with type 1 diabetes and remaining endogenous insulin reserve may benefit from treatments aiming at preservation of insulin secretory capacity but any pharmacological intervention will likely 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, preferably double-blind and placebo-controlled and should include patients with 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) or, if appropriately justified, the percentage of patients with C-peptide increases above a clinically meaningful threshold 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 or with a relevant reduction in insulin requirements. Any of these endpoints not included as co-primary endpoint should be evaluated as important secondary endpoint. Other secondary endpoints should include fasting and postprandial blood glucose concentrations, 24-hour glucose profiles and total daily insulin requirements. Occurrence of ketoacidosis should be recorded. 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. Again, a step down approach within the paediatric population is recommended (see 7.1). 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 7.1.

7.3. Delay in onset/prevention 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/prevention 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. 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 are considered appropriate primary endpoints. If glucose-lowering agents are investigated, a wash-out phase of appropriate duration (e.g. at least 3 months) is needed prior to the efficacy evaluation to exclude a masking effect on diabetes. The observed effect will need 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 risk’ but ’disease free’ persons. In this context it should also be recognized that IFG/IGT and type 2 diabetes are

different stages of the same disease continuum and that treatment of such subjects could be considered as an initiation of treatment in an earlier stage of the disease rather that preventing the disease. Until further clarification of this issue and if the test agent is intended for long-term treatment (e.g. 'early treatment' with glucose-lowering agents), the primary endpoint will need to be supported by additional data showing benefit with regard to microvascular and/or macrovascular complications. 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.

Definitions

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). (Paediatric OGTT dosing 1.75 grams/kg to maximum dose of 75 grams glucose)

  OR

- HbA1c ≥ 6.5% (48 mmol/mol). (The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay, ADA recommendation)

Impaired glucose tolerance (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).

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

Hypoglycaemia

Hypoglycaemia in adults

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 the classification published by the International Hypoglycaemia Study Group (Diabetes Care 2017, 155-157):

- **Severe hypoglycaemia:**

  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.

- **Clinically important hypoglycaemia:**

  A glucose level of less than 3.0 mmol/l (54 mg/dl) with or without typical symptoms of hypoglycaemia is considered sufficiently low to indicate serious, clinically important hypoglycaemia.

- **Glucose alert value:**

  A glucose alert value less than 3.9 mmol/l (70 mg/dl). This need not to be reported routinely in clinical studies, although this would depend on the purpose of the study. It should be noted that glycaemic thresholds for responses to hypoglycaemia vary and thus symptoms of hypoglycaemia can occur at higher glycaemic levels, in particular in patients with poor glycaemic control. Therefore the use of other additional glycaemic thresholds and capturing of symptoms suggestive of hypoglycaemic symptoms can be considered.

Hypoglycaemia in children

ISPAD suggest the following categorization.

There are no clinically important reasons to distinguish between mild and moderate hypoglycaemia, and younger children will almost always need to be treated by a parent or caregiver. Therefore, mild and moderate hypoglycaemia are considered together.

- The child or parent is aware of, responds to, and treats the hypoglycaemia orally after documenting a BG level of ≤ 3.9 mmol/l (70 mg/dl). The ADA has suggested using the terminology of ‘Documented Symptomatic Hypoglycaemia’ for this category.
- Asymptomatic hypoglycaemia applies when the child is not symptomatic with hypoglycaemia but the BG is documented to be ≤ 3.9 mmol/l (21).
- The category of asymptomatic hypoglycaemia, especially if <3.6 mmol/l (65 mg/dl), is suggested because it is important to recognize the frequency of hypoglycaemia unawareness or glucose values that place an individual at risk for hypoglycaemia unawareness.
- Severe hypoglycaemia

  The child is having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma, has convulsions and may require parenteral therapy (glucagon or i.v. glucose). ADA suggests using 3.9 mmol/l (70 mg/dl) as the definition of hypoglycaemia in all age groups for research purposes to maintain consistency in reporting hypoglycaemia.