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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 current EU regulatory position on the main topics of the clinical development of new medicinal products in the treatment or prevention of diabetes type 1 and type 2. The latest revision refers mainly to an update of the safety section with respect to cardiovascular (CV) safety (referring to the Reflection Paper on assessment of cardiovascular safety profile of medicinal products), but also updated guidance concerning estimands, requirements for monotherapy indications, studies in children, 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 autoimmune 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 insulin replacement therapy, extensive education and disease management. Prevention of complications and management of pregnancy are important issues. Despite advances in insulin therapy and in technologies to administer insulin and monitor blood glucose, it may still be challenging to reach recommended outcomes.

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 one new pharmacological intervention 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.

Diabetes, especially type 2 diabetes, is frequently associated with overweight, hypertension and dyslipidaemia, making multiple cardiovascular risk factor intervention a key issue. Therefore, global treatment goals 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). In addition, for some medicinal products for the treatment of diabetes, a reduced risk of macrovascular complications has been documented.

It should also be noted that the discrimination between type 1 and type 2 diabetes may not always be straightforward (see relevant guidelines from ADA, EASD and 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.

These notes are intended to assist applicants during the clinical development phase. Potential deviations from guidelines should be explained and justified in the Marketing application

Insulin delivery systems (including pumps, autoinjectors, prefilled syringes, etc.) and insulins with a novel route of administration are outside the scope of this document. Insulins with a novel route of administration are not within the scope of this guideline. In such cases EMA scientific advice is recommended. 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 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:

- Guideline for good clinical practice - EMA/CHMP/ICH/135/1995 (ICH E6[R2]);
- ICH Guideline E8 (R1) on general considerations for clinical studies – EMA/CHMP/ICH/544570/1998 Corr*;
- Note for Guidance on Studies in Support of Special Populations: Geriatrics - CPMP/ICH/379/95 (ICH E7) and Questions and Answers - EMA/CHMP/ICH/604661/2009 (ICH E7 Q&A);
- 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) and Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials - EMA/CHMP/ICH/436221/2017 (ICH E9[R1])
- Note for Guidance on Population Exposure: the extent of population exposure to assess clinical safety - CPMP/ICH/375/95 (ICH E1);
- Note for Guidance on Ethnic Factors in the Acceptability of Foreign Clinical Data CPMP/ICH/289/95 (ICH E5) - and Questions and Answers CPMP/ICH/5746/03 (ICH E5[R1]);
- Guideline on Clinical Investigation of Medicinal Products in the Paediatric Population EMA/CPMP/ICH/2711/1999 (ICH E11[R1]);
- 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;
- 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 medicinal products (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 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 will in general result in a balance across most factors but stratified randomisation 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).

4.2. Assessment of efficacy

4.2.1. Efficacy criteria/Treatment goals

Treatment of patients with type 2 diabetes should aim at improving blood glucose concentrations and reducing the risk of both micro- and macrovascular complications. Even though the primary aim of the confirmatory studies with medicinal products for the treatment of diabetes is to demonstrate a favourable effect on blood glucose control, it is also important to consider effects of the product 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 correspond to a reduction of the long-term risk of development of microvascular complications. Therefore, HbA1c is an appropriate primary endpoint.

Estimation of the treatment effect (estimands)

The primary target should be the estimation of a treatment effect based on the difference in HbA1c from baseline to the end-of-trial (or another predefined timepoint) between the test compound and a control treatment. The actual adherence to treatment as well as intercurrent events should be reflected in the estimation of the effect. The main expected intercurrent events to be considered include treatment discontinuation, additional medications and rescue medication.

Treatment discontinuation

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 (treatment policy strategy).

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 to be used for the treatment-policy strategy. In case data are missing after treatment discontinuation, appropriate missing data imputation methods would have to be applied.

Additional/rescue medication

Considering introduction of other medication that will influence HbA1c values, 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).

In this scenario, statistical modelling, i.e., an appropriate missing data imputation method would have to be applied. However, standard imputation methods or modelling targeting a hypothetical estimand strategy may not be appropriate if based on subjects that do not require rescue medication or if based on the missing-data-assumption, since these subjects differ from those who require rescue medication. Modelling based on data obtained in the placebo group might be an acceptable approach to target a treatment policy strategy to reflect discontinuation from treatment and a scenario in which additional medication was not introduced.

For active controlled trials with a non-inferiority (NI) hypothesis, the same primary estimand strategy as outlined above might be justified. However, in the presence of missing data, uncertainty about the underlying missing data mechanism requires the application of a conservative estimation procedure. Since an estimation procedure may be conservative in a superiority setting but not in a NI setting (or vice versa), a NI comparison may require a different estimation procedure than a superiority comparison even if the same estimand is targeted. Furthermore, it is likely necessary that a supplemental estimand is specified to address the impact of important intercurrent events like protocol violations and deviations.

The effect should be further estimated by analysing the difference in proportion of patients who reached an absolute HbA1c value of e.g., ≤ 7 and/or 6.5 % (≤ 53 and/or 48 mmol/mol) at end-of-trial without the use of rescue medication and who remain adherent to treatment.

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

Pre-specified, combined endpoints, e.g. reflecting the percentage of patients achieving target HbA1c without hypoglycaemia, can be informative as secondary endpoints for products aiming at lowering the risk of hypoglycemia. .

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.

4.2.2.2. Plasma glucose and other glycaemic endpoints

Change in fasting plasma glucose 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), glucose AUC, variability in glycaemia (time in range measured by continuous glucose monitoring (CGM)) and nocturnal hypoglycaemia could also be relevant endpoints depending on the mode of action of the test agent and risk for hypoglycaemia in the study population. Strategies to handle intercurrent events when estimating the effect of treatment on these variables can be the same as for HbA1c.

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 suitable. Serum fructosamine can also be used as an endpoint in short-term studies.

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 of efficacy.

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 CGM is encouraged and regarded as useful in both adults and children to describe glucose profiles.

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

In insulin-treated type 2 diabetic patients, 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.

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, heart rate, and/or other relevant biomarkers should be documented.

A new medicinal product for the treatment of diabetes should preferably show a neutral or beneficial effect on factors associated with cardiovascular risk. 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. 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 medicinal product on the 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 approval.

If statistically robust 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.

4.2.5. Patient-reported outcomes

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

Furthermore, such information will help to contextualize observed effects on measures derived from CGM such as glucose variability, glucose excursions and time spent in range.

4.3. Study Design

4.3.1. 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 are also 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.

4.3.2. Pharmacodynamics

Although there are no specific requirements for pharmacodynamic testing of medicinal products for the treatment of diabetes, 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.

4.3.3. 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. Considering that on- and off-target effects may follow different dose-response relationship selecting the optimal dose could benefit from including multiple, including off-target, PDfactors in the dose selection process. Additional information in support of dose selection can also be obtained through modelling and simulation.

For therapeutic exploratory studies, a parallel, double-blind placebo-controlled monotherapy design is recommended. If an add-on claim is intended, dose ranging can be studied as add-on to first line therapy. In dose-ranging studies, at least 3 dosages should be studied with a total treatment phase of at least 8 weeks.

Glucose based metrics 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.

4.3.4. Confirmatory studies

4.3.4.1. General design elements

Parallel-group, randomised, double-blind, 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.

and

- Superiority of the new agent over placebo when added to background therapies, which represents established therapies 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. 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% (3 mmol/mol) is generally considered acceptable. If non-inferiority cannot convincingly be demonstrated, it is necessary to balance the degree of the observed or potential inferiority against other clinical advantages documented in the development program regarding e.g., safety, tolerability, compliance, and/or improvement in cardiovascular risk profile or risk of long-term complications.

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 4.2.3)

A washout period is recommended in patients previously having received medicinal products for the treatment of diabetes 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.

In the maintenance period, the dose(s) of the medicinal products (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.

4.3.4.2. Requirements for monotherapy indication

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. Use of placebo for more than 6 months is generally not recommended.

Candidates for these trials should preferably have a relatively low starting HbA1c. 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 are 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.

4.3.4.3. Requirements for add on indication

There are many possible therapeutic combinations of agents for the treatment of diabetes. The choice of which combinations to study should be made based on recommendations for diabetes treatment from learned societies (e.g. EASD, ADA, ISPAD) as well as on known potential safety issues for some combinations. To support the general claim "add on to other medicinal products for the treatment of diabetes" efficacy data would be expected for combinations with medicinal products representing standard of care. In addition, combinations for which specific safety issues (e.g., hypoglycaemia) are expected (based on mechanisms of action) should be investigated. Study results from all combination studies will be reflected in the product information (SmPC section 5.1).

Add-on studies should be placebo- or active-controlled. It is recommended:

(i) To select patients not meeting therapeutic targets on an 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 an established agent (background therapy) for 8-12 weeks and thereafter, if therapeutic targets are not met, 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 maximum effect.

(iii) To avoid dose adaptation of the background therapy throughout the study, unless this is necessary for safety reasons.

4.3.4.4. Combinations with insulin

Combination therapy of medicinal products for the treatment of diabetes with insulin may occur in different clinical situations and patient populations. Most frequently, insulin therapy is introduced in

patients inadequately controlled on other medicinal products for the treatment of diabetes. In this case, some of the previous products may be discontinued when insulin is initiated. However, patients already receiving insulin may also benefit from adding another product. Reasons for such consideration may be, for example, severe hypoglycaemic events preventing the desired level of glycaemic control or insulin-induced weight gain in already obese patients.

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 medicinal products for the treatment of diabetes) 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.

4.4. 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 influence the response to a particular medicinal product for the treatment of diabetes. Those potential factors should 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.

4.4.1. Elderly

Regarding the elderly, it is important to determine whether 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 older 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.

4.4.2. 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 (e.g. 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 evaluating efficacy and safety should be carried out. However, extrapolation of efficacy data in young adults to adolescents and/or younger children may be possible to a limited extent, if appropriately justified and pre-specified. Safety data may also to some extent be extrapolated, but there may be a need to follow long-term safety after approval of a paediatric indication.

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 diabetes development in children is 13 – 14 years, it is recommended that trials are performed in patients aged 10 to 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, at least for medicinal products with a novel mechanism of action, it is recommended that studies in children/adolescents are only initiated once sufficient safety and efficacy data from adult trials are available. If significant safety concerns (based on data from adults) 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.

4.5. Safety aspects

4.5.1. General considerations

As for any other medicinal product, the occurrence of a wide spectrum of adverse effects should be carefully monitored and documented in detail for a new agent. Special efforts should be made to capture potential adverse events that could be related to 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).

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.

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.

4.5.2. 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 given level of self-monitored blood glucose (see also sections 5.6.1 and 8). 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 by age: ≤ 65 years, 65-74; 75-84 and 85+ 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 CGM, providing more complete information on night profiles is recommended.

4.5.3. 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 where the safety profile is 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).

4.5.4. Immunogenicity

If the new agent is a protein, development of anti-drug antibodies should be addressed 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).

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 medicinal product for the treatment of diabetes (see section 4.1) also apply to insulin preparations. Both type 1 and type 2 diabetic patients should be studied, especially since dose recommendations and hypoglycaemia risk are expected to differ. Randomisation will in general result in a balance across most factors in the study groups but stratified randomisation may be helpful e.g. with respect to types of previous insulin regimens. Specific populations should be considered (see section 4.4).

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 medicinal product for the treatment of diabetes 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 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 potentially during the night) are necessary, particularly in type 1 diabetic patients. CGM often provides more meaningful results and is preferred if possible.
- 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), time in range, hypoglycaemia or other clinically meaningful outcomes.

Weight gain is frequent in diabetic patients trying to implement intensified insulin therapy. The evolution of body weight will also be taken into account in the global evaluation of efficacy and safety.

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.

5.4. Study design

5.4.1. Pharmacokinetics

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 diabetes patients, adults and children (stratified by age), and in various situations associated with PK variability: insulin dose, site of

injection and thickness of 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 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.

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. However, differences in parameters of PK/PD activity cannot be used to claim superiority over a comparator unless the differences translate into improved 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 endpoint is the 24-h blood glucose profile.

5.4.4. Therapeutic confirmatory studies

General considerations regarding the design of confirmatory studies, described in section 4.3.4, also apply here. However, the use of a placebo is usually not ethical in insulin-dependent diabetic patients. Therefore, studies will generally include 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, adolescents and younger adults, clinical studies for insulin preparations are normally required in the paediatric population, unless otherwise justified. Particular attention should be paid to the occurrence of hypoglycaemia and optimal dose titration. However, as described for other agents (see section 4.4.2) 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, time in range and hypoglycaemic episodes are important secondary endpoints (see section 5.3) that should be documented, preferably, by CGM.

5.6. Safety aspects

5.6.1. Hypoglycaemia

Hypoglycaemia is the largest 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).

In order to assess glucose variability and nocturnal hypoglycaemia, the use of CGM devices is recommended. 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 the lower incidence of hypoglycaemia is not associated with increased HbA1c with the investigational agent.

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. 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 IGF-1 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 (higher than EU-wide standard of 100 units/ml concentration) and fixed combinations of insulin with other non-insulin injectable medicinal products for the treatment of diabetes, 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 adjust 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 other injectable medicinal products for the treatment of diabetes 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, and hyperglycaemia may be associated with variable percentages of beta cell loss. 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, achieving glycaemic goals can be hampered by the risk of severe hypoglycaemia. Patients with type 1 diabetes may therefore benefit from new therapies that, in addition to insulin, improve glycaemic control and/or reduce the risk of hypoglycaemia.

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 in HbA1c from baseline 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. Additional secondary endpoints may be considered if scientifically justified (e.g., time in range measured by CGM).

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 and mitigated during the studies.

7. Other potential claims

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 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) (see section 8, ADA definition of type 1 diabetes stages).

Pharmacological intervention studies that aim to delay or prevent the onset of type 1 diabetes should preferably 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. Studies suggest that the risk of developing type 1 diabetes within the next 5-10 years is highest in subject with multiple autoantibodies. Further risk stratification within autoantibody positive individuals can be made utilizing measures of glucose tolerance or beta cell function.

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. Observations such as reversal of dysglycaemia, improvement in glucose tolerance, or preservation of beta cell function would also support efficacy. Genotyping may be important for treatment success.

A step-down approach within the paediatric population may be proposed, i.e. commencing studies in younger age groups after efficacy and particularly relevant safety data are available from older subjects (e.g. 12-<18 y., 6-<12 y.; 1-<6 y.). In the age group below one year, monogenic diabetes forms need to be excluded.

Not all subjects with stage 1 or stage 2 type 1 diabetes will eventually develop the clinical stage 3 disease (see section 8 for definitions), 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 any observed effect, 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.

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

Patients with type 1 diabetes and remaining endogenous insulin reserve may benefit from treatments aiming at preservation of insulin secretory capacity. However, 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 in patients with a diagnosis of type 1 diabetes (stage 3 (see definition in section 8)) should be randomized, 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:

1. 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, and
2. HbA1c, frequency of hypoglycaemic episodes, particularly severe events

The percentage of patients with a relevant reduction in or absence of insulin requirements could be of interest. However, any statistically significant reduction of the total insulin dose will need to be justified from the perspective of clinical relevance.

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 via continuous glucose monitoring (CGM) 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 likely 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 any observed effect 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 is 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.

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 lifestyle interventions. Risk definition and criteria need to be pre-defined using widely accepted tools for diabetes risk assessment. The type and enforcement of appropriate lifestyle 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 and placebo-controlled. In addition, appropriate lifestyle 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.

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 in 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 at 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 any observed effect should be discussed and carefully balanced against the risks of the intervention.

For assessment of efficacy; see also section 4.2 concerning definition of the scientific question of interest.

8. Definitions

8.1. Diabetes

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

- Random plasma glucose concentration ≥11.1 mmol/L (200 mg/dl)

  OR

- Fasting plasma glucose ≥7.0 mmol/L (126 mg/dl), Fasting is defined as no caloric intake for at least 8 h

  OR

- 2-h plasma glucose concentration after 75 g anhydrous glucose in an oral glucose tolerance test ≥11.1 mmol/L (200 mg/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 (126 mg/dl)

  AND

- 2-h plasma glucose concentration ≥ 7.8 and<11.1 mmol/l (140 and 200 mg/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 impaired fasting glucose should not be diagnosed on a single glucose measurement but needs confirmation.

Stages of Type 1 diabetes (ADA 2023)

Stage 1; Multiple islet autoantibodies, no IGT or IFG.

Stage 2; Multiple islet autoantibodies, IFG and/or IGT

Stage 3; Islet autoantibodies may become absent, diabetes diagnosis by standard criteria

8.2. Hypoglycaemia

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 the classification published by the International Hypoglycaemia Study Group (Diabetes Care 2017, 155-157 and Pediatr Diabetes 2022, 1322–1340):

- **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.

- **Hypoglycaemia alert value:**

  A glucose level 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.