28 June 2012
EMA/444348/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	NL comments
2	Johnson&johnson
3	Daiichi Sankyo
4	EASD
5	F. Hoffmann-la Roche Ltd.
6	EFPIA
7	Merck Sharp & Dohme (MSD)
8	EMA
9	JDRF
10	Swissmedic

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418□8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
6	EFPIA welcomes this second revision of the CHMP Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (DM), which is quite positive. EFPIA believes it will be beneficial to optimise the development of medicinal products for the treatment and prevention of diabetes. EFPIA also welcomes the adoption of global definitions in the draft, including the definition of hypoglycaemic event, with reference to the American Diabetes Association Workgroup on Hypoglycaemia - Defining and Reporting Hypoglycaemia in Diabetes, Diabetes Care 2005. This current draft guideline includes many of former industry comments. There are however still some sections, where more details, clarifications and change of requirements would be helpful: 1. The current draft guideline includes a new section (6.2) on the development of drugs for preservation of beta cell function in type 1 DM. However this is also relevant to type 2 DM. EFPIA recommends adding corresponding guidance or revising the current type 1DM section to clarify what should be common or different features in drug development depending on the intended target patient population. 2. The previous version, 20 January 2010, of the guideline included a section (6.2) on glucose lowering agents aiming at slowing the progression of diabetes complications. However, this has been deleted in the current draft apart from a brief mention in section	Preservation of beta cell function in type 2 DM is also investigated in the context of prevention/delay in onset of diabetes, which is already addressed in the guideline. Currently, preservation of beta cells as primary goal of treatment in patients already diagnosed with T2DM (leading to a respective indication) is not foreseen and beyond the scope of the guideline The previous sections on diabetes complications need thorough revision, which will be performed at a later time point

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	4.1.4. Specific recommendations on micro and macrovascular complications are therefore missing. The macrovascular complications may be sufficiently covered in other sections of the current draft, however EFPIAs recommend incorporating the previous guidance or something similar regarding retinopathy, nephropathy and neuropathy or pointing to guidance where advice on development within these important complications is given.	
	3. Sections on the need for placebo control (4.1.7., 4.2.1 and 4.2.2) need to be clarified and changed accordingly. Just placebo controlled studies should not be mandatory in phase 3 as the study population at this stage should represent the broad target population in terms of severity of diabetes and co-morbidity especially from a CVD perspective. Such a population is not suitable for long-term placebo controlled studies. It should be acceptable to perform either placebo or active controlled confirmatory studies as appropriate.	Placebo- and active controlled studies should be part of the clinical development. Attempt to make this clearer.
	4. Placebo control should never be required when testing new insulins in type 1 as well as in type 2 patients (section 5.3.3). EFPIA suggest this to be reflected in the guideline.	Agreed to remove placebo-control. It is acknowledged that placebo-controlled trials are difficult even in T2DM patients not yet fully insulin-dependent. In addition, performance of the test insulin should always be compared to that of an established insulin with similar pharmacokinetic profile.
	5. EFPIA supports the concept that although evidence of the absence of a cardiovascular risk should be provided at the time of Marketing Authorisation Application (MAA), the actual type and amount of data and stage of submission with respect to MAA	

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	review should be based on product specific preclinical and early clinical signals as well as on an effect of the drug on cardiovascular risk factors 6. Sections on requirements for testing the immunogenic potential are missing in both section 4 and 5. It is suggested that this is included for glucose lowering agents for both type 1 and type 2 DM, including duration of studies.	Has been addressed.
9	1. As detailed in Specific Comments, Section 6.1 Delay in onset / prevention of type 1 diabetes mellitus fails to take into account our increasing ability to stratify subjects and stage progression in the type 1 diabetes at-risk setting that can be used for design of clinical trials. Initial prevention clinical trials will need to use intermediate endpoints rather than prevention of type 1 diabetes. Both primary and secondary prevention trials will need to be considered and will have unique issues. 2. As detailed in Specific Comments, Section 6.2 Preservation of beta-cell function in patients with new onset type 1 diabetes mellitus fails to take into account our increasing understanding of new onset type 1 diabetes. Significant residual beta cell mass may be present beyond 3 months after diagnosis and therapeutics may be able to preserve such mass in a clinically meaningful manner. The primary endpoints outlined for clinical trials in the new onset setting and the length of duration of treatment benefit need further consideration as detailed below.	Although this is true, the current focus of drug development is on subjects at high risk for developing type 1 diabetes, which is driven by considerations regarding feasibility of clinical trials (to show a relevant effect) and potential safety concerns of investigational drugs. Although remaining beta cell reserve is likely to be highest short after diagnosis of type 1 diabetes (and thus chances for successful treatment), the potential for longer-lasting relevant beta cell reserve is acknowledged. The 3-month period has been deleted.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 332 and following	1	**Comments:** The following text has now been added to the section on add-on studies: *"To support the general claim "add on to oral antidiabetic agents" efficacy data would be expected for combinations representing standard of care as well as for combinations for which the additive effect could be expected to be limited (i.e based on mechanisms of action)."* In general, we support this simplification of the indication. However, this general claim may be misleading, especially for new classes of drugs, as it may suggest that efficacy and safety has been demonstrated in combination with all other oral glucose lowering drugs. Therefore, section 5.1 of the SmPC should include a text on combinations that have been investigated.	Accepted.
Line 540 and following	1	**Comment:** In this section there is an emphasis on cardiovascular safety, while other safety concerns, such as cancer risk, for example, get little attention. **Proposed change (if any):** Line 549 and 550 should be inserted at the beginning of section 4.4.3.3	Accepted

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Line 442 and following (General considerations)	1	**Comment:** Alignment between pre- and post-approval studies is recommended. **Proposed change (if any):** Please add after line 457: Given that the clinical development of diabetes products increasingly will be followed by PASS studies as part of an RMP, pre-emptive alignment between pre- and post-approval studies is recommended	Accepted
Line 735 and following (Delay in onset / prevention type 1 diabetes)	1	**Comment:** it is likely that most treatments will consist of immunosuppressants or immunomodulators. These treatments are potentially dangerous, especially in young children, and many subjects at increased risk for developing type 1 diabetes will eventually not develop the disease. Therefore, studies should be limited to high risk patients.	Already stated.
151	2	"The pharmacological activity of the main metabolites should be quantified, in diabetic patients when possible (in relevant animal models otherwise), and studied in detail if they are likely to contribute substantially to the therapeutic or toxic effects" – This statement does not really make sense – is it intended that the PD activity of metabolites should be studied in patients? This would be a considerable undertaking. Clarification	Accepted.

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		should be made on whether this is a typographical error and what is meant is that metabolites should be quantified in diabetes mellitus patients or alternatively the information that the Agency would anticipate would be collected.	
157	2	Further clarification should be provided on the extent of PK information that would be anticipated within the diabetes mellitus patient population. e.g. is it anticipated that a wide variety of diabetes mellitus patients sub-populations must be studied or would this be determined on a drug / mechanism of action basis.	Not accepted. The relevant information is included in other guidelines
190	2	Further clarification should be provided for glucose AUC setting e.g. is this AUC for the 7-point, for an MMTT or would other AUC be acceptable?	Not accepted The text implicates that different types of AUC would be acceptable considering that this is a secondary endpoint
199	2	Further clarification should be provided on when continuous glucose monitoring should be used e.g. in what settings, what endpoint and to support what type of therapy	Partially accepted It is clarified that CGM should be considered, depending on the mechanism of action of the test agent (and thus on its propensity to cause hypoglycaemia) and the risk of the study population for hypoglycaemia.
202	2	It is suggested that reference to blood pressure changes as a result of the tested agent be included into Section 4.1.4 or section 4.1.5 other measures of metabolic status or cardiovascular risk factors.	Not accepted. This is included in section 4.1.5.
205	2	Well validated methods for improvement of beta cell function are cited, however no guidance is provided as to which endpoints are considered here. Further details should be provided.	Not accepted. It will be up to the Applicant to justify
205	2	Further details should be provided on whether it is	Accepted.

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		anticipated that the sponsor would need to demonstrate that the endpoint is well-validates or whether the CHMP consider specific endpoints to be well validated. Information should be included on which endpoints the CHMP consider to be well validated.	
215	2	The term “partly neuropathy” should be more clearly defined.	Accepted
227-231	2	**Comment:** With regard to balance of population with respect to gender. Later sections speak to the need for cardiovascular risk assessment in new development programs. Subject population, with appropriate inclusion criteria for T2DM, at higher CV risk will be skewed towards more males. So “balance” itself will be difficult **Proposed change (if any):** Adequate numbers of females should be included in the development program to assess efficacy and safety	Recognized, more male patients will be accepted if justified. It is nevertheless important that the treatment groups are balanced with regard to gender to avoid bias.
247	2	**Comment:** placebo controlled monotherapy A1c less than 8.5% is too restrictive. Rescue criteria that are progressive over the initial 6 months will prevent subjects from experiencing prolonged periods of poor control. Clinical trial effect will also positively benefit these subjects **Proposed change (if any):**	Not accepted The cut off is not strict; “e.g. 8.5%”. It is also stated that “Although the use of strict rescue criteria could be an argument to also allow inclusion of patients with high baseline HbA1c in studies with a duration of more than 3 months, this may lead to a high drop-out rate with subsequent difficulties in interpreting the study results.”

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		10%	
254	2	**Comment:** supporting efficacy assessment should be the proportion who are withdrawn for the lack of efficacy or have received rescue therapy, not just those who have withdrawn for lack of efficacy **Proposed change (if any):** Add in those receiving rescue therapy to be used in the support of efficacy assessment	Accepted.
265	2	It is stated that if only an add-on indication is planned, dose range finding can be done as add-on. Clarification is requested on whether it is the CHMPs position that this would not support dose selection for monotherapy studies. The current text could potentially imply that separate studies are required for mono and add-on therapies. Clarification should be provided on whether this was the intent of the text and also whether a dose range finding study in monotherapy must be done, if both mono- and add-on indications are planned? **Proposed change (if any):** Include text to indicate that 1 dose-ranging study as mono or as add-on supports phase 3 dose selection for mono and add-on indications.	Accepted and clarified
268	2	Section 4.2.1 Therapeutic exploratory studies (dose finding): Comment is made re the primary endpoint of	Accepted and clarified

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		studies 8-12 weeks in duration vs > 12 weeks (ie FPG vs HbA1c, respectively). It would seem likely that both endpoints would be obtained in studies of 12 weeks duration, and that use of HbA1c as the primary endpoint for a 12 week study would be the Sponsor's risk. Furthermore, the duration of study for which HbA1c should be used as a primary endpoint appears to be in slight contrast to what is included in section 4.3.2.2 Children and adolescents – Efficacy assessment, where HbA1c is recommended as the primary endpoint for studies of at least 12 weeks.	
292	2	Text should be included to align with the "EMA Implementing the European Medicine Agency's Roadmap to 2015: The Agency's contribution to Science, Medicines, Health" indicating that measurement of the patient perspective should be considered in studies of patients with diabetes mellitus.	Difficult to see how this fits in this section of the guideline. However, patient-reported outcomes based on validated tools can always be included as secondary endpoints.
299	2	Line 299 states "Even though HbA1c could be acceptable as primary endpoint, other efficacy measures such as effects on micro and macrovascular endpoints would be taken into account before such an indication would be considered approvable." Clarification should be provided on whether the Agency anticipates monotherapy indications would require the demonstration of benefit on micro- or macrovascular disease as such a requirement would be unwarranted in the absence of a safety signal.	Not accepted. To show a positive effect on macrovascular disease an outcome study would be needed Whether it would be needed for a first line monotherapy indication would depend on the magnitude of the effect on HbA1c in comparison to metformin and the amount and type of safety information available.
382	2	Insulin dose (eg. 0.5 units/kg) used as an example is	The example suggesting a dose of at least 0.5 U/kg/day has

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		too high. There are patients on significantly lower doses of insulin that are not well controlled, but their total daily dose is limited by hypoglycaemia. Would suggest not using an example, but simply stating that insulin doses have been optimized by the health care provider, and control remains inadequate.	been removed.
404	2	Presentation of data for elderly. The subgroup proposed for subjects > 85 would be expected to have very few subjects. Suggest the age groupings of 65 – 75 and > 75 would be more appropriate for the diabetes mellitus population.	Not accepted The cut-offs are in line with the ICH E7 Q&A
788	2	The choice of the primary endpoint (AUC C-peptide) makes sense – however, since trials are intended to minimize differences in A1C, A1C is not an appropriate endpoint. New onset T1DM patients have a low incidence of severe hypoglycaemia – and any differences would 2-4 years to see. Similarly, differences in other clinical endpoints listed are likely the result of long/large studies, and unlikely to be seen in trials that demonstrate definitive and substantial preservation of beta cell function (C-peptide AUC). Maintaining this language and implementing this regulatory requirement will have a seriously negative impact on efforts to find effective therapies for T1DM. Moreover, it is not likely that most therapies will be tried in prevention of T1DM until preservation of beta cell function is demonstrated. So, regulations that make development for preservation of	To make sure that the observed amount of improvement in stimulated C-peptide translates into a clinically relevant benefit, additional parameters need to be investigated. For this purpose, the guideline provides a choice between HbA1c, hypoglycaemia or percentage of subjects that are insulin-free or have a relevant reduction in insulin requirements, which is considered adequate. The B/R assessment will put into context the magnitude of the effect as well as the safety profile of the test drug.

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		beta cell function in T1DM very difficult will have a negative effect on efforts to find therapies that prevent T1DM. We would urge the Agency to reconsider this approach, as it will prevent useful therapies for T1DM from being developed.	
77-80	3	**Comment:** This sentence requires modification, since in most current guidelines the 'wait and see' policy with diet and exercise has been replaced by early and immediate treatment with metformin. The clinical experience shows, despite the fact that stringent diet and exercise could reverse pre-diabetes, in daily practice it is not manageable for the greatest part of the patients. The guideline should reflect the treatment dilemma in daily practice.	Not accepted Diet and exercise should be tested, but it is not stated for how long. Thus, the text is not in conflict with an early initiation of drug treatment. It should be considered that inclusion of patients with poor lifestyle measures may inflate the placebo-effect, which may lead to an apparent decrease in the placebo-adjusted effect size of the test agent.
82	3	**Comment:** Insulin resistance and resulting hyperglycemia should be mentioned as a major part of the 'metabolic syndrome' as well. At least hyperglycemia should be referred as part of the deadly quartet.	Not accepted. Diabetes is hyperglycaemia
86	3	**Comment:** The last sentence should be revised in that respective evidence for beneficial effects on macrovascular risk would require extremely long observation periods (see UKPDS).	Not understood, no request for outcome studies in this section
151	3	**Comment:** We wonder, whether it would be useful to include a sentence on the definition of a relevant drug. Is	Accepted

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		metformin or a SU a relevant drug for all glucose lowering agents, or should a similar MOA be referred, if a drug has been offered to the market already?	
171	3	**Comment:** We wonder based upon the recent discussions by ADA/EASD and other groups involved, whether HbA1c should be and stay the only gold standard/primary parameter for glucose control. The guideline should be open to accept other measurements in addition as co-primary factors, as scientific discussion is ongoing.	Not accepted HbA1c is still considered as the primary endpoint of choice. Other glycaemic measures can be included as secondary endpoints and will be evaluated during the marketing-authorisation procedure.
202	3	**Comment:** We would encourage the inclusion of blood pressure measurements at baseline/study end in addition.	Not accepted. Covered in 4.1.5
Paragraph: 4.2.1. Therapeutic exploratory studies (dose finding): page 8	3	**Comment:** For explorative studies when novel MoAs are investigated, also in diabetes area, adaptive designs for instance with multiple dose treatment arms could be considered to test multiple dosing and then narrowing these down during the course of the adaptive study. Whilst the use of placebo in phase 2 (superiority claim) is important, wash out periods and placebo use at this stage of development should be considered more carefully in patients with a more advanced stage of diabetes. Accordingly and as per comments received from EU Ethics Committees, the use of placebo for 2-3 months is acknowledged to put study subjects at unnecessary risk of high glucose control and worsening	Not accepted The guideline is a recommendation. Alternative programmes for phase 2 studies could be acceptable, but cannot be covered by the guideline. In the case of alternative development plans, a CHMP scientific advice is recommended. Wash-out is not needed for long-term trials. In all clinical trials appropriate and pre-defined rescue criteria should be in place to ensure that patients are not objected to poor glycaemic control for prolonged periods of time.

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		of related complications. For a new anti-diabetic agent under development with an established MoA (i.e an agent acting on improvement of insulin resistance; or an agent working on the beta cell level as an insulin sensitizer), exploratory studies should include in their design an established active comparator with similar MoA (this would limit development of many `me too agents` within the same therapeutic class). Development for an `add on` claim during phase 2 (lines 265-266) should be discouraged. A new anti-diabetic agent firstly should at this stage of development explore and prove its efficacy as monotherapy treatment and the scope of this phase is primarily focusing on dose finding. Such an `add on` claim may apply to phase 3 confirmatory studies, should the clinical development progress towards registration. This would give a better understanding of glucose lowering effectiveness of a newly tested agent with also short-term data on safety and tolerability (no confounding factors from any other anti-diabetic agent should be included). Metformin can remain for the time being as the most utilized active treatment comparator in these non-inferiority claim studies: metformin today is considered as `first line therapy` in most of the type 2 diabetes patients' worldwide (standard of care).	
280	3	"Use of an established active comparator" should give more details with respect to what is regarded as a	Accepted.

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		suitable established active comparator: Met and or SU or preferably a drug with a similar MOA, if already on the market?	
Paragraph 4.2.2.1. Monotherapies studies: page 9 Line 293ff	3	**Comment:** In phase 3 studies the use of placebo should now be avoided. A placebo controlled study has already been carried out in phase 2 (paragraph 4.2.1 of this guideline already requests this). There is no need for a placebo controlled study to be repeated in phase 3. Also as further consideration, in these studies there are minimal chances of detecting clinically relevant changes of micro and macrovascular outcomes at endpoint, as typically studies in phase 3 are usually not long enough to detect such differences versus baseline within and between treatment arms (the sentence on lines 300 and 301 should be removed). **Proposed change (if any):** Line 308: it should be stated here that the run-in period depends on the half life (wash out period) of previous utilized anti-diabetic treatments. Lines 311-316: Whilst there is a mention of `encouraging` up-titration of a newly tested agent at this stage of development, there is no reference to the potential need of down-titration (in case of tolerability emerging issues) of the dose of a new compound (with the exception of line 322 for the maintenance phase	Not accepted It is stated in 4.2.2 that “monotherapy study of no less than 3 months duration, which could be a dose-ranging study using $HbA1_C$ as the primary endpoint, or the inclusion of a placebo arm for 3 months at the beginning of an active controlled trial” Investigation of hard endpoints is not requested in monotherapy studies. It is evident that we would accept different durations of wash out depending on the MOA Downtitration is possible in case of safety concerns, most commonly hypoglycaemia, and should be well documented.

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		only). This might also be required.	
Paragraph 4.2.2.2. Add on or combination studies: page 10 Lines 325 ff	3	**Proposed change (if any):** Line 331:Please add on to: `...guidelines from learned societies (e.g. EASD; ISPAD; ADA) and suggest to include also: `country-specific scientific societies guidelines, where applicable`, because sometimes they might differ in some countries compared to others in Europe (this is necessary particularly when ECs require so).	Not Accepted Products are approved in EU and therefore country specific guidelines cannot be applied
Paragraph 4.2.2.3. Combinations with insulin: page 11 Lines 374-7	3	**Comment:** The timing of starting a combination treatment (insulin plus an oral agent) has always been an ill defined area in clinical development for type 2 diabetes (see the definition of `secondary failure` for sulphonylureas). The Agency should clarify this through the new guidelines. A definition of the most appropriate timing to start insulin in combination with one or more anti-diabetic oral treatments needs to be clearly defined in this guidance (i.e. by referring to existing scientific guidelines; or for instance stating that `patients are suitable to be enrolled in an insulin combination therapy if their glucose control remains above 8% in the last three months at the highest doses given of one/more glucose-lowering agents; or more simply agreeing that: `secondary drug failure can be defined as mean diurnal blood glucose >12 mmol/L after an initial good response of ⩾2 years). The UKPDS study showed that after 6 years of disease, 44% of patients	Usually, insulin is initiated in patients failing on other glucose-lowering agents but some physicians/diabetes groups believe that insulin therapy should be introduced early in the treatment course. There are several disease and patient factors that need to be considered and therefore the decision on insulin therapy should be individualised and remain in the hands of the treating physician. The current guideline should not be mistaken as treatment guideline. In order to cover the full spectrum of patients expected to be treated with an insulin combination, 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. Only accepted change: addition of elderly patients to represent the full range of the target population.

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		developed secondary failure. Since then, the targets of glycemic control have become increasingly stringent, so secondary failure of oral hypoglycaemic drugs now occurs much sooner than in the past: clinical advanced symptoms are persistent hyperglycaemia, weight loss and ketonuria. Ultimately through these guidelines, patients enrolled in development studies should be identified and criteria of enrolment standardised across development programs. In addition, studies should consider the different situation in younger and older diabetics: the important point here is the early introduction of insulin in studies with younger diabetics, as the lifetime risk of complications of young type 2 diabetics is great. On the other hand, older patients who are not symptomatic and have no microvascular complications such as retinopathy, can be allowed to remain in `secondary failure` at an HbA1c of 8-9%. In these patients, prognosis is governed mainly by macrovascular disease, which is not greatly influenced by glycemic control. Studies in type 2 diabetes should reflect these diversities. Ultimately these guidelines should help the industry to explore this area of application further in phase 3 of clinical development.	
Line 368	3	**Comment:** The use of insulin should not be regarded as last option only. Some diabetes groups prefer to introduce insulin early as an option of beta cell preservation.	Not accepted. The guideline does not exclude the possibility to introduce insulin early in the treatment course (see comment above).

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		Therefore, add-on to insulin should be regarded as valid therapy in diabetes as well and beyond getting control of uncontrolled patients also reduction of insulin, e.g. by reduction of insulin resistance or by recovery of beta-cells could be a highly valuable therapeutic option. It should not be excluded from the guideline.	
Paragraph 4.4.3. Long-term safety and cardiovascular safety: page 13-16 Lines 480-481:	3	**Comment:** The guidelines currently state that `it is essential, as far as possible, to exclude that the new drug increases the risk of macrovascular complications, e.g. cardiovascular disease`. In consideration of the fact that even a 3-5 years study might not be sufficient to show any difference in terms of primary prevention, this statement is not of great help. It would be better if the guideline had clarified the concept by emphasizing the need of looking, for instance, at the worsening of an existing cardiovascular profile in patients with type 2 diabetes after a defined number of years of the disease (CV secondary prevention study only). It is basically unlikely, unless a clear early safety CV signal is detected and its magnitude agreed, to explore the impact on CV safety even in such a quite long period of time during a CV outcome clinical study (there is in fact in this regard a high risk of under-powering the study due to high drop-out rate over time and also because of lower than predicted rate of Major CV Events: MACE).	Not accepted The text clearly states what is expected

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89	4	**Comment:** No reference to reduced macrovascular risk in T1DM.	Accepted
97		**Comment:** Here monogenic and other genetic forms of diabetes are mentioned with no prior indication of the heterogeneity of DM. It may be useful to give some number here (90% T2DM; 5% T1DM; 5% all other remaining forms including monogenic and other genetic forms of diabetes).	Accepted.
109	4	**Comment:** delay in onset or prevention of diabetes mellitus or improvement of insulin sensitivity and/or preservation of beta-cell function in patients with pre-diabetes and diabetes. In other words I would introduce here insulin resistance as a target for therapy together with beta-cell dysfunction and opening toward pre-diabetes.	Not accepted Inclusion of improvement in insulin sensitivity in the scope of the guideline not accepted since this has not been identified as primary objective in clinical trials relevant for licensing.
195	4	**Comment:** Although use of devices for continuous glucose monitoring may be encouraged I would also comment they should not be used as primary endpoint but limited to specific outcomes (nocturnal glucose profiling, glucose fluctuations ...).	Accepted. Have not been considered as primary endpoint.
Para 4.1.4	4	**Comment:** Wondering if NASH/NAFL could be introduced here as another measure of metabolic control/status.	Not accepted Not enough scientific support
Para 4.1.5.	4	**Comment:** Consider introducing associated microvascolar risk	Not accepted. Reflected in 4.1.4

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		factors.	
Para 4.1.7.	4	**Comment:** With an increasing number of class of antidiabetes drugs is placebo still a valid comparator?	Yes, but we only require a 3 month study, which could be a phase 2 study
Para 4.2.1.	4	**Comment:** I would spend a word with respect to duration of wash-out as this may be quite different from one drug to another.	Not accepted. Different durations would be accepted if justified
Para 4.2.2.1.	4	**Comment:** I'm wondering how it can be possible to have a monotherapy study showing an effect on microvascular endpoint: this would require a large sample size and a very long follow-up since only early stages of the disease may be treated with monotherapy. Proxy of microvascular complications should be considered (microalbuminuria?...)	Misunderstanding, no hard endpoints required, has been clarified
306	4	**Comment:** Same comment as for Para 4.2.1	See above
Chapter 4.3	4	**Comment:** Predictor of drugs response may require post-hoc analysis and meta-analysis as it looks difficult, at least to me, to see this done on a prospective manner. Therefore, it should be stated whether meta-analysis or pooled-data analysis can be acceptable for such a purpose.	Not accepted This is not a requirement. Applicant can come up with different types of analyses
445	4	**Comment:** How elevated? 2x, 3x or more the upper limit values?	Not accepted No need to be specific in this guideline with respect to this
473	4	**Comment:**	Acknowledged. Balanced wording is included in the guideline.

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		I would be careful in putting too much emphasis on CSGM as its use is limited in time and, therefore, potentially misleading.	
513	4	**Comment:** How is the “suspicion” defined? Consider introducing some reference point as done by FDA. I believe it is important to avoid over interpretation of data which may change the cut off for “suspicion”.	Acknowledged, but suspicion leaves some flexibility which would be lost if the guideline is too specific
518	4	**Comment:** I have a mixed feeling with recruitment of individual at very high CV risk as, being the most vulnerable ones; they can be exposed to unwanted risk not just because of the specific features of the drug under evaluation but simply because of intensification of blood glucose lowering strategies.	Acknowledged
521	4	**Comment:** Consider requesting in long term studies collection of data on the “neglected” microvascular complications.	This section refers to safety
Para 4.4.3.2	4	**Comment:** See comment on line 518.	See above
Para 4.4.3.3	4	**Comment:** Data on cancer could be included as well.	Accepted
Chapter 5	4	**Comment:** General comment. New insulin formulation will be more and more associated with new devices for injection. I wonder whether and how this should embedded here.	Not accepted. Injection devices are beyond the scope of the guideline.
250	5	**Comment:**	Accepted

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		Proposed change (if any): Although the strict rescue criteria or study withdrawal criteria for poor glycemic control could be an argument to also allow inclusion of patients with high baseline HbA1c in studies with a duration of more than 3 months….	
Lines 841 to 851	5	**Comment:** It would be helpful to specify what 'additional data' could be considered as supportive data for the delay in onset of T2DM. As well, it would be useful to specify that cardiovascular risk factors should be monitored as safety measures for therapies. **Proposed change (if any):** Cumulative diabetes incidence or time to diagnosis of diabetes according to established diagnostic criteria is considered an appropriate primary endpoint. However, the effect needs to be statistically significant as well as clinically relevant. Delaying the onset of diabetes may be important but it is currently unclear how much delay would be necessary to convey a reduction of microvascular or macrovascular complications, the real purpose of a pharmacological intervention in 'at risk' but 'disease free' persons. Until further clarification of this issue, the primary endpoint will need to be supported by additional data (such as prolonged improvement in HbA1c levels, weight loss, LDL levels	Not accepted. The important endpoints for demonstration of benefit of an intervention in 'at risk' but 'disease free' subjects are mentioned in the guideline. Sponsors are free to define additional endpoints in their clinical trials. Blood pressure and serum lipids could be both efficacy and safety endpoints.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		or other CV risk markers) showing potential long-term benefit with regard to microvascular and/or macrovascular complications, particularly in case of intended long-term treatment (e.g. 'early treatment' with antihyperglycaemic agents). Cardiovascular risk factors such as blood pressure and serum lipids should also be monitored as safety measures for therapies. Assessment of markers/tests of beta-cell function/decline may be included to further support the preventive nature of any observed effect.	
lines 873 to 880	5	**Comment:** Inclusion of the definition for pre-diabetes based on HbA1C in accordance with ADA Standards in Medical Care of Diabetes published 2011 **Proposed change (if any):** Increased risk for diabetes (pre-diabetes) based on HbA1C 5.7–6.4%	Not accepted since this is controversial. WHO does not consider HbA1c to be a suitable diagnostic test for diabetes or intermediate hyperglycaemia (the term 'pre-diabetes' is discouraged)
82	6	**Comment:** Hyperlipidemia should read dyslipidemia as HDL is low. **Proposed change (if any):** Overweight, hypertension and dyslipidemia are often associated with diabetes mellitus.	Accepted
90-106	6	**Comment:** This section is not very useful. **Proposed change (if any):**	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is suggested to delete the section and make a reference to guidelines issued by ISPAD	
146-148	6	**Comment:** Section 4 now includes all glucose lowering agents (except insulin). As Injectable peptides are also part of this section, a section on product immunogenicity would be useful. See General Comments section.	Is now reflected in the safety section
158-159	6	Investigating all types of patients may not be needed, some extrapolation of PK information may be appropriate. **Proposed change (if any):** Initial PK studies can be done in healthy volunteers, it is important that PK studies also be ***considered*** ~~performed in~~ ***for*** all types of patients for whom treatment is intended (including children and elderly) ***and PK studies performed as appropriate***.	Not accepted. Indeed it may not be assumed that the PK properties observed in healthy subjects will be the same in diabetics and at different age groups. Any extrapolation would need sound scientific justification.
179-181	6	**Comment:** The HbA1c absolute value of ≤ 7 and/or 6.5 % is suitable for the adult population. However, as indicated in the ISPAD clinical practice consensus guideline 2009, chapter 7, the target should be ≤ 7.5% in children and adolescents. This guidance only operates with HbA1c in percentage. There is a new unit on its way and already implemented in many countries and that is mmol/mol.	Not accepted Efficacy in children has a separate section Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This needs to be reflected if we still use % or mmol/mol in measuring Hba1c. **Proposed change (if any):** "The applicant should also justify the clinical relevance of the effect by presenting responder analyses comparing the proportion of patients who reached an absolute value of ≤ 7 and/or 6.5 % ***in adults and ≤ 7.5% in children and adolescents*** across the different treatment groups (ref. ISPAD).	
181-182	6	**Comment:** Is it possible to utilise clinically significant responder definitions such as proportion of patients achieving HbA1c goal without hypoglycaemia, or composite endpoints of HbA1c, weight loss and blood pressure? **Proposed change (if any):** Other definitions of a responder, ***e.g. such as the proportion of patients achieving HbA1c goal without hypoglycaemia, or using composite endpoints of reduction in HbA1c, weight loss and blood pressure,*** should be prospectively identified and justified by the applicant.	Acceptable as secondary endpoint.
199-201	6	**Comment:** Currently, continuous blood glucose (CGM) is not standard clinical practice in the treatment of diabetes and there is a lack of experience with CGM from investigators as well as parents/patients in case of	Acknowledged. Wording has been modified

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		paediatric use. Continuous blood glucose monitoring may generally be used as supportive information and should not be a specific requirement. It is suggested to change the wording to: In addition, independently of the drug class investigated, would such data still be considered optional (in case mechanism of action suggests low risk for hypoglycemia) or what would be considered the minimum requirement for generation of data by continuous blood glucose monitoring and nocturnal measurements, especially in the paediatric population? **Proposed change (if any):** However, depending on the mode of action and risk for nocturnal hypoglycaemia, continuous blood glucose monitoring may provide ***additional information*** ~~be needed~~, especially in the paediatric population.	
206-209	6	**Comment:** "*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…".* In insulin-treated Type 2DM patients, a delay in the start of insulin treatment could also be considered as a relevant measure of efficacy. In addition, reduction in insulin doses alone should be	Partly Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		allowed as a secondary endpoint for efficacy. Same goes for C-peptide as a measure of beta cell function **Proposed change (if any):** In insulin-treated type 2 DM patients, the entire elimination of the need***/less need*** for insulin in a clinically meaningful proportion of patients, or a relevant reduction in insulin dose accompanied by a clinically significant improvement in the evolution of body weight or reduction in hypoglycaemic events could be considered as a relevant measure of efficacy, in addition to improvement in HbA_{1C} ***or maintaining a targeted HbA1c***.	
215	6	**Comment:** Suggests to delete: "partly" **Proposed change (if any):** Long term complications include macrovascular (coronary, cerebrovascular, and peripheral vascular diseases) and microvascular complications (retinopathy, nephropathy, and ~~partly~~ neuropathy).	Accepted
244-246	6 + 7	**Comment:** The characterization of "early stage of disease" as "less than two years after diagnosis" is of concern. First, it is widely accepted that the time of onset of type 2 diabetes is difficult to determine, and that most patients with type 2 diabetes have had the underlying disease for many years. Secondly, restricting placebo-	Partly accepted. However, patients with a long duration of diabetes are no obvious candidates for monotherapy. Therefore, it is considered appropriate to investigate the test agent as monotherapy in patients with a more recent (known) onset of disease. The placebo controlled study could be a phase 2 dose-ranging study (clarified in section 4.2.2)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		controlled monotherapy studies to individuals who have only been diagnosed with type 2 diabetes for less than two years will not provide an adequate assessment of the efficacy and safety of a medication in patients with longer duration disease, and presumably more profound beta cell dysfunction. Third, given the uncertainty regarding the onset of disease in an individual patient carries with it uncertainty regarding the underlying pathophysiologic status (with respect to beta cell function, insulin resistance, etc). Finally, the underlying concern regarding the ethics of placebo-controlled studies should not logically exclude patients with short duration of disease, as compared to patients with longer-standing disease. Study design elements which protect patients against prolonged periods of severe and clinically meaningful hyperglycemia should be considered the primary method for ensuring patient safety and ethical study conduct. **Proposed change (if any):** Please be referred to the general comments no 3.	
253-255	6	**Comment:** *"A reduction in the proportion of patients who are withdrawn due to lack of efficacy compared to placebo according to study protocols may be used to provide additional support for efficacy".*	Not accepted. This refers specifically to the placebo controlled studies

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): This sentence would fit more appropriately in section 4.1.4 (reworded to not only focus on the comparison to placebo).	
262, 272	6	**Comment:** It may be impossible to conduct double-blind trials if the investigational drug and comparator are injected using different devices. This needs to be taken into considerations.	Accepted. , double-blind is the recommended design
262	6	**Comment:** Suggests that active controlled studies should be allowed from dose finding studies - as this will give you the comparative effectiveness that is so important from a MA perspective and still give the different dose efficacies.	In dose-finding studies a placebo arm is considered relevant for estimation of the effect size. Sponsors are free to also include an active comparator.
262-267	6	**Comment:** *"A parallel, fixed-dose, double-blind placebo-controlled monotherapy design has proven useful in evaluating new drugs. …."* We see no rationale/justification for requesting dose-finding studies by default by monotherapy. We are not aware of any precedence where the dose response curve is skewed in the add-on setting. The default use for new agents is add-on to metformin. *"If only an add-on claim is requested, dose ranging can be studied as add-on to first line therapy (e.g. metformin)".* Clarification is requested if a	Accepted and clarified Monotherapy design is the recommended design to evaluate the genuine effects of the test agent. If only an add-on claim is requested, dose ranging can be studied as add-on to first line therapy.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		monotherapy indication can be requested based on data from Phase III, even if the dose-ranging study has been conducted as add-on therapy (e.g. to metformin).	
268-270	6 + 7	**Comment:** Assessment of HbA1C effects, especially in the context of dose-range finding studies, can be adequately performed at 12 weeks of treatment (and indeed, most of the HbA1C efficacy is evident, and separation between doses can be ascertained after 8-10 weeks for most therapeutic classes). The guidance that HbA1C only be used for study "more than 12 weeks duration" should be reconsidered. **Proposed change (if any):** FPG should be the primary criterion for studies less than 12 weeks in duration. HbA1C should generally be the primary criterion of studies that are 12 weeks or greater in duration, unless pharmacokinetic or mechanism-related concerns are present.	Accepted.
272	6	**Comment:** A double blind design is preferable, however not always feasible, i.e. when investigating drugs for parenteral use. It is suggested to change the wording to: **Proposed change (if any):** Parallel-group, randomised, double-blind, placebo and	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		comparator-controlled studies should be performed. It is acknowledged that some route of administrations may be an obstacle to complete blinding designs.	
Line 274-277 Line 295-297 Line 456-457	6	**Comment:** Please consider moving the first bullet from section 4.2.2. to section 4.2.1. in order to indicate that studies of short duration and investigating dose range are exploratory investigations. Where an add-on indication only is planned, i.e. metformin + new product, it is encouraging to see that dose ranging is acceptable in an add-on study only and a monotherapy study is not required. However, this is inconsistent with 4.2.2 and 4.2.2.1 that suggests superiority of a new agent over placebo in at least one monotherapy study of no less than 3 months is required even if no monotherapy claim is being pursued. It should not be necessary to establish the genuine glucose lowering effect of the agent alone since this is not the intent of the application. The efficacy of the additional product can be assessed in a placebo and an active comparator add-on study. The safety profile of first line agents is well established and, therefore, safety of the new agent can be derived from an add-on study versus placebo and the active comparator study and a monotherapy study should not be necessary.	Not accepted It has been made clearer that the monotherapy study can be a phase 2 study. However, since this is still considered as important for the confirmation of the effect the bullet point will not be moved. The assessment of the genuine favourable and unfavourable effects of a new glucose-lowering agent is considered important. Interactions with other agents in combination studies may blur the picture.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): 4.2.2. 1st bullet Please delete “monotherapy” Superiority of the new agent in at least one ~~monotherapy~~ study of no less than 3 months duration 4.2.2.1 monotherapy studies Placebo controlled monotherapy studies ~~are always~~ may be required to evaluate the genuine glucose lowering effect and safety profile of the new agent, independent of whether the marketing authorisation is intended for monotherapy or add-on therapy in cases where the efficacy and safety can not be deduced from placebo or active comparator add-on studies.	
285	6	**Comment:** The non-inferiority margin of 0.3% seems low in some instances even when the EMA guidance' on non-inferiority is adhered to. Such studies require a very high number of patients and 0.4% can often be justified. A reference to CHMP “Guideline on the choice of the non-inferiority margin”, 2005 should be referred to. It is recommended changing the recommended margin to 0. 3-0.4 % in accordance with the guidance from FDA. **Proposed change (if any):** A margin of 0.3***-0.4%*** is generally considered as	Not accepted. Considering the generally lower baseline HbA1c values in more recent clinical trials and the limited effect of some new compounds with respect to lowering of HbA1c, the non-inferiority margin of 0.3% is considered appropriate. Any widening of the margins should be properly scientifically justified.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		acceptable.	
297-301	6	**Comment:** *"In addition, a monotherapy study comparing the test drug to metformin is always needed if an indication for first line monotherapy is intended. Even though HbA1c could be acceptable as primary endpoint, other efficacy measures such as effects on micro and macrovascular endpoints would be taken into account before such an indication would be considered approvable."* This text is confusing; such a study is typically 6-12 months and includes a couple of hundred patients; it is difficult to envisage how that could provide information on micro- or macrovascular endpoints. Furthermore, this request/statement is not in line with advice on lines 216-217 emphasizing the demand for proper large scale and long term controlled trials when evaluating effects on micro- and macrovascular endpoints. **Proposed change (if any):** Clarify that only micro- and macrovascular surrogate endpoints (lipid levels, blood pressure, albumin excretion, etc...) can be evaluated in these kinds of trials. Or provide justification why the effects on micro- and macrovascular endpoints will be considered specifically for a monotherapy indication. A more detailed guidance on how effects on micro- and macrovascular endpoints should be collected and	Accepted, has been clarified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		analysed in case a monotherapy indication is intended would be preferred, and how this differs from the programme needed if add-on indications is intended.	
307-308	6	For confirmatory studies a washout is not always needed due to the long duration of such study. **Proposed change (if any):** 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 long duration a wash out period may not be needed***.	Accepted
317-318	6	**Comment:** It is inconsistent if it is required to use placebo for more than 6 months and at the same time the upper limit of placebo trials are set to 6 months (which is agreed to). At the same time the request only "well controlled failures" in these trials, which is in conflict with the statement of having a broad representation of patients in the phase 3 programs (which also is agreed to).	Not accepted. The broad representation of patients in the phase 3 programs does not refer to patients who are not well controlled on current treatment (unless due to intolerance).
319	6	**Comment:** "an original mechanism of action" – Please clarify if “original” means new.	Accepted
320-322	6	**Comment:** "In the maintenance period the dose(s) of the antihyperglycaemic agent(s) (investigational drug,	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		background therapy, comparator) should be kept stable unless a dose reduction is necessary for safety reasons." This is in the monotherapy study section. There should be no concomitant anti-diabetic background treatment. If it refers to non anti-diabetic concomitant treatment, it is impossible to keep it stable during a long term clinical trial. Flexibility should remain for adjustment of the concomitant background therapy after a certain period at the discretion of investigator, not only for safety reason but also for any reason deemed to be in the subjects' 'best interest'. For example, patients may need an adaptation to their blood pressure treatment. It would be particularly important to take this into consideration for long-term controlled studies In addition, why is the word "antihyperglycemic agent" used instead of "glucose lowering agent" which is the term used in other parts of the guideline? **Proposed change (if any):** ~~In the maintenance period the dose(s) of the antihyperglycaemic agent(s) (investigational drug, background therapy, comparator) should be kept stable unless a dose reduction is necessary for safety reasons. Dose changes and reasoning should be well documented.~~ ***glucose lowering agents used as***	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		concomitant background treatment should be kept stable during the study unless adjustment is necessary for safety reasons or for any reason deemed to be in the subjects' 'best interest' according to the investigator. Any change in background treatment that may affect the efficacy or safety evaluation should be appropriately documented and reported.	
325	6	**Comment and suggestion for change:** It is suggested to get clarification on when add-on - and when combination can be claimed.	Accepted.
325	6	**Proposed change (if any):** Suggests a heading change to: 4.2.2.2 Add-on (or combination) studies ***except insulin products***	Accepted
332	6	**Comment and suggestion for change:** Suggests that OAD is replaced by GLA in this guidance as GLP-1 analogues and other non-insulin proteins fall under this category.	Accepted
332-334	6	**Comment:** *"To support the general claim "add on to oral antidiabetic agents" efficacy data would be expected for combinations representing standard of care as well as for combinations for which the additive effect could be expected to be limited (i.e. based on mechanisms of action)."* What is the intent of testing combinations with limited effect? If the mechanisms of action do not predict a	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		limited effect, would testing still be required? This requirement seems to indicate that all possible combinations must be tested. However, if clinically significant safety issues are suspected from a certain combination, a small and short study might be appropriate to evaluate the combination from a safety point of view as a basis for warnings and precautions in label (similar to DDI studies). **Proposed change (if any):** Delete the request to study combinations that are expected to provide limited efficacy. It should be sufficient to study the relevant/appropriate combinations (based on Mode of Action and standard of care); the label text will reflect what has not been studied and that information should be sufficient to help prescribers.	
332-334	6	**Comment:** This section 4 pertains to all glucose lowering agents (except insulin), so include for example GLP-1 agonists. Could a general claim “add on to GLP-1 agonist agents” apply?	The term ‘oral antidiabetic agents’ has been changed to ‘gucose-lowering agents’ to also include GLP-1 agonists.
332-334	6	**Comment:** To date no anti-diabetic molecules have been given a general claim “add on to oral anti-diabetic agents” although insulins may have similar language in section 4.2 of the SmPC. If this may be a potential indication	Acknowledged and clarified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		for future anti-diabetic medications, further guidance should be provided on the circumstances under which such an indication would be granted. If this is intended to provide guidance for the development of insulins, this should be clearly specified or moved to the appropriate section.	
335-336	6	**Comment*:*** *" For add-on studies, the combination of the new agent and the established agent should be compared to the established agent alone."* We would like to understand the rationale for placebo to be included in all add-on trials. **Proposed change (if any):** For add-on studies, the combination of the new agent and the established agent ~~should~~ ***could*** be compared to the established agent alone ***(placebo control) or to an active control. The applicant is expected to submit at least one placebo-controlled and one active-controlled trial.***..	Accepted
353	6	**Comment:** "If the HbA1c improvement over placebo is of doubtful clinical relevance, comparison with a commonly used combination is advisable in order to put into perspective the improvement obtained with the new combination". This is an ambiguous sentence, please clarify.	Accepted and clarified
360-362	6	**Comment:**	Not accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A scientific consensus on first line combination therapy as a pre-requisite is considered a big hurdle for development as it essentially excludes new drug classes from first line combination therapy. Any clarification on the supporting data package that could support a 1st line combination indication would be helpful. **Proposed change (if any):** Description of requirements for data on efficacy and safety for first line combination, e.g. factorial studies as required by the FDA, required comparator... Suggestion of patient populations who may benefit from initial combination therapy (e.g. those with higher starting HbA1c values).	A scientific consensus on first line combination therapy would be needed
379-384	6	**Comment:** Could the Agency clarify if a study with one specific insulin would support the general claim "combination therapy with insulin" (i.e. for all insulins)? Could the Agency also clarify that it only refers to basal insulins? Please confirm that "combination therapy with insulin" claim can be obtained based on one study only designed according to this section. Although the Agency agree that most commonly insulin is added on the GLA the Agency still request for the design where the investigational drug in a placebo controlled situation is added on insulin plus metformin.	No requirement for the use of a specific insulin is foreseen. Both patients on basal insulin only and patients on basal-bolus regimens may be included, if stratified. As in clinical trials with other glucose-lowering agents, rescue criteria should be predefined to ensure that patients will not sustain prolonged periods of poor glycaemic control. The study described in the guideline is recommended. Other study designs are principally possible but companies are advised to seek EMA scientific advice.

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		This requires a fixed insulin/metformin dose in 26 weeks. As an alternative, the design with 3 arms: Insulin, investigational drug alone and the combination and then base the efficacy on dose difference should be acceptable for claiming "combination therapy with insulin".	
382	6	**Comment and suggestion for change:** This trial design also needs to address those patients that may be on an other GLA (than metformin) since they cannot use metformin (e.g. due to reduced renal function)	Included.
389-391	6	**Comment:** Would a composite response criterion of no./% of patients achieving target HbA1c with no hypoglyceamia be acceptable as a primary objective for an add-on to insulin study? Such an endpoint could be also considered as a valid primary endpoint. **Proposed change (if any):** The primary objective of the study should be to demonstrate that the test drug is superior to placebo in HbA1c reduction ***or using a composite response criterion such as the no./% of patients achieving target HbA1c with no hypoglyceamia***. Secondary endpoints should, amongst others, include frequency of hypoglycaemia with focus on severe events, change in body weight and in insulin do	HbA1c is considered the appropriate primary endpoint to assess efficacy of a glucose-lowering agent. Other endpoints such as hypglycaemia, change in bodyweight or, as suggested, % of patients achieving target HbA1c with no hypoglycaemia should be considered as secondary endpoints.
Line 397-399	6	**Comment:**	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		How should the requirements for lifestyle and diabetes care similar to EU member states be appropriately judged by the sponsor of a clinical development program? With lifestyle and diabetes care becoming rather comparable to EU in at least some Asian countries, and further considering increasing multiethnicity in the EU population, how would proven efficacy in Asian patients be judged for an EU approval? It would be helpful to list those countries that the CHMP have lifestyle and diabetes care which is similar to the EU. In addition, according to ICH E5 all regions require sufficient patients who are ethnically representative of the local population. The requested share of at least 30% trial population to be representative for EU seems to be a bit artificial and may be a matter of differing interpretation. By specifying a number as high as 30% it is difficult to satisfy this requirement for all ICH regions in a single development programme. It is thus recommended to amend the text. **Proposed change (if any):** With regards to the characteristics of the trial population it should be considered that a significant number of patients (i.e. at least ***20-***30%) should be included from EU countries or countries with lifestyle	The listing of countries would be very difficult and would be subject to change over time. The specific mentioning of 30% has been replaced by “a relevant number of patients”.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and diabetes care similar to those of EU member states ***(e.g. North America, Australia, New Zealand…)***.	
Line 400	6	**Comment:** It should be acknowledged that recruitment of patient 85+ in phase 3 studies in order to show efficacy and safety in this age may be a challenge. As per the previous draft we recommend that the top age category be >75 yrs with guidance what constitutes sufficient number of subjects and duration of exposure. In addition, please see for consistency, page 18 where it is mentioned: < 65 and > 75 It is also suggested that the Agency refer to ICH guideline E7 and its Q&A. Population PK data must be sufficient and should be recommended. **Proposed change (if any):** Therefore, data should be presented for various age groups (~~65-74; 75-84 and 85+~~ ***>65 years and >75 years***) to assess the consistency of the treatment effect and safety profile in these patients with the non-geriatric patient population.	Not accepted The cut offs are in line with the E7 and its Q&A.
410-414	6	**Comment:** The safety concerns highlighted in the guidance document are very difficult if not impossible to evaluate in a one year study as recommended in	Not accepted The safety concerns are only given as examples

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Section 4.3.2.2. It is suggested to remove specific examples of safety concerns as (as pointed out in the guidance) these concerns will vary based on the drug Mechanism of Action. **Proposed change (if any):** *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.*	
420	6	**Comment:** As per the regulation, PDCO requires trials in patients 10 to less than 18 years of age. **Proposed change (if any):** Currently, the incidence and prevalence of Type 2 DM 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 yr old.	Accepted.
425	6	**Comment:** Section 4.3.2.2 suggests that an extension phase of	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		40 weeks is needed in paediatric studies. This assumes a 12 week primary endpoint; however in cases where there is a controlled period of longer duration, this would result in a requirement for greater than 12 months exposure. This should be clarified. **Proposed change (if any):** Completion of an extension phase ~~of 40 weeks~~ ***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.	
429	6	**Comment:** Adding diet and exercise to a clinical trial may add bias/noise to trial results. It is thus suggested to delete line 429-430 since this is considered to be standard practise.	Not accepted As it is standard practice and implemented in all treatment arms it will not introduce bias
476-481	6	**Comment:** It is suggested that there is a reference from section 4.1 to this section regarding cardiovascular. In addition, to improve clarity, it is suggested to split section 4.4.3 into two separate sections: • Long term safety • Long term cardiovascular safety	Not accepted The section is considered rather clear
590	6	**Comment:** Please harmonise terminology in this section (short, rapid, intermediate and long-acting).	Accepted
596-599	6	**Comment and suggestions for change:**	Not relevant for the type of studies requested

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The Agency definition of premixes and fixed combinations does not distinguish between "mixes" of different physical forms of the same active ingredient vs. a co-formulation of two active substances. Suggest that antibody formation is considered, and the guideline adjusted to take the need for antibody data into consideration, i.e. 1 year study.	Section amended
Line 602	6	**Comment:** This section currently mentions measures of glycemic control but cross refers to section 4.2.2 Therapeutic confirmatory studies. Should this in fact cross refer to 4.1.3 Measures of glycemic control? **Proposed change (if any):** The measures of glycemic control detailed in the section pertaining to other glucose lowering agents also apply to insulin preparations (see ~~4.2.2~~ 4.1.3).	Accepted
Line 619-620	6	**Comment and suggestion for change:** Please clarify that only data from type 1 diabetes is required in clamp studies- and do they need to be from European patients? **Proposed change (if any):** …..in the response to insulin, ~~particulary in type 1 diabetes,~~ pharmacodynamic data in type 1 diabetes are of primary importance….	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 625-626	6	**Comment:** In the guideline is PK required in all type of patients. As mentioned in comments to line 156-159, the same comments apply here. The request for PK data must depend on the PK profile of the investigational drug, including data from modelling and simulations. **Proposed change (if any):** "PK studies should be considered for all types of patients."	See comment above.
Line 644	6	**Comment and suggestion for change:** Please clarify relevance of better HbA1c seen in the light of the treat-to-target designs are generally used. Stating that "differences in PK/PD should not be used to claim superiority unless associated with better HbA1c or other etc." is not understood, as treat to target is the preferred study design.	Any claim of superiority (to be reflected in the SPC) needs to be based on statistically significant and clinically relevant improvement in glycaemic control or other patient relevant parameters.
Line 646	6	**Comment and suggestion for change:** It is suggested that the treat to target design is described in section 5.3.3, as the treat to target design is useful design when investigating insulin products.	Is considered self-evident for an insulin but has been included for clarity.
Line 654-658	6	**Comment and suggestion for change:** Cross-over studies should not be recommended in long term trials as there will be carry over effect on metabolic control which makes data unuseful! Such design can only be used in PK/PD studies of a	Long-term cross-over studies are not recommended in the guideline but proposal has been included for clarity.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		minimum numbers of injections. This should be clearly stated here.	
Line 654-658	6	**Comment and suggestion for change:** For insulin products, treat to target is a useful design to be used in the exploratory studies. This is proposed to be mentioned also in section 5.3.3.2.	See comment above
Line 660	6	**Comment:** This section currently cross refers to 4.3.3. This should be 4.2.2. **Proposed change (if any):** General considerations regarding the design of these studies, described in section ~~4.3.3~~ 4.2.2, also apply here.	Accepted.
Line 664	6	**Comment and suggestion for change:** The text is not clear. Please confirm that "combination therapy with insulin" claim can be obtained based on one study only designed according to this section.	See comment above
Line 668-670	6	**Comment and suggestion for change:** Run-in periods are used for various reasons and may not always be needed. It is suggested to delete this section.	Not agreed. Stabilisation of insulin dose and glycaemic control is another important goal.
Line 687-688	6	**Comment:** This section states that studies with insulins are required in the paediatric population unless otherwise justified. This could be interpreted as being required for approval. However in section 5.5.4 the need for sufficient safety data prior to starting paediatric	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		studies is acknowledged which may make inclusion of paediatric data at initial submission unfeasible without incurring delays to submission of the adult data. The guideline should be modified to be consistent between sections and to provide further guidance on the desired timing of paediatric studies. **Proposed change (if any):** Since type 1 diabetes predominantly develops in children and adolescents, clinical studies for insulin preparations are usually required in the paediatric population, unless otherwise justified. However sufficient safety data in adults should be available prior to commencing paediatric studies (see section 5.5.4) and therefore paediatric development may be deferred where appropriate.	Accepted
Line 703-705	6	**Comment:** The Agency states that "A relevant reduction of documented episodes of severe hypoglycaemia (see 7.2), if studied in appropriately controlled trials, could itself form the basis for approval of a new treatment". EFPIA suggest that it is not limited to severe hypoglycaemia only. A percentage reduction in symptomatic hypoglycaemia, or in the composite of hypoglycaemia symptomatic episodes and confirmed low continuous glucose monitoring excursions, should also be acceptable as a basis for approval.	The wording has been amended to clarify that 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 as comparator. The effect size considered to be clinically relevant needs to be justified and depends on the frequency and severity of events observed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		What percentage reduction in (a) severe hypoglycaemia and (b) symptomatic hypoglycaemia would be considered clinically meaningful? **Proposed change (if any):** A relevant reduction of documented episodes of severe hypoglycaemia, symptomatic hypoglycaemia or composite of hypoglycaemia symptomatic episodes (see 7.2), if studied in appropriately controlled trials, could itself form the basis for approval of a new treatment".	
711-713	6	**Comment:** Please note that it may not always be feasible to estimate endogenous insulin production, so please change the wording. **Proposed change (if any):** … and endogenous insulin production should be assessed, where possible.	Accepted
Lines 714-715	6	**Comment and proposed change:** It is completely unknown which level of "higher affinity for IGF-1R" has any kind of clinical relevance for retinal adverse reactions. IGF-1 mediated retinopathy is considered to be based mainly on paracrine stimulation, thus extrapolation to systemic effect is questionable. EFPIA suggests that the Agency reflects this information in the guideline.	This is a recommendation. Would be up to the company to justify.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 722-733	6	**Comment:** It is unclear whether these studies of insulin in children would be required prior to approval of the product in adults (as is suggested in the section discussing other antihyperglycemic therapies). This should also be clear that these requirements apply to both type 1 and type 2 DM patients. **Proposed change (if any):** …..paediatric studies in type 1 and 2 DM should preferably be carried out when sufficient safety data in adults are available and studies of insulin in children will generally not be needed prior to marketing authorization.	See comment above.
Line 807	6	**Comment:** Header, 6.3 should include (vis a vis 6.1) prevention to state: Delay in onset/prevention of Type 2 DM Both section 6.1. and 6.3. should have the "prevention" included: 6.1. Delay in onset / prevention of type 1 diabetes mellitus **Proposed change (if any):** 6.3. Delay in onset / Prevention of type 2 diabetes mellitus	Accepted
Line 846-849	6	**Comment:** "*Until further clarification of this issue, the primary*	The wording has been amended to further clarify that this applies to intended long-term treatment. Such potentially

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		endpoint will need to be supported by additional data showing benefit with regard to microvascular and/or macrovascular complications, particularly in case of intended long-term treatment (e.g. 'early treatment' with antihyperglycaemic agents)." Typically, pre-diabetic subjects have an even lower CV risk and risk for diabetes complications than overt diabetics. Therefore, such a requirement for outcomes data may not be feasible to perform due to the very large size and long duration. **Proposed change (if any):** No excess CV risk should be sufficient together with reasonable evidence for no other safety issues.	indefinite treatment of 'at risk' but 'disease free' subjects needs to be properly justified by demonstrating a clinically relevant benefit.
Line 850	6	**Comment and suggested change:** A description of recommended and accepted markers would be appreciated.	Not accepted. To be justified by companies.
Line 860	6	**Comment:** 7.1 Definitions Diabetes and prediabetes definitions are inconsistent (diabetes def. acc to ADA/WHO crit, prediabetes def. acc to IDF crit), it is suggested to expand on rationale.	Definition of diabetes is consistent. The term 'prediabetes' is discouraged.
Line 873	6	**Comment: Typo** Proposed change: "Impaired ~~glucosetolerance~~ ***glucose tolerance*** (IGT):"	Accepted
Lines 873-880	6	**Comment:** Impaired glucose tolerance and impaired fasting	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		glucose should also not be diagnosed on a glucose measurement but needs confirmation.	
Line 878	6	**Comment:** "Fasting plasma glucose 6.1 to 6.9 mmol/l [110 to 125 mg/dl]" This is in disagreement with the recent ADA lower cut-off of 5.6 mg/dl but there is no worldwide consensus. As this is an EU document it might be expected that the Agency sticks to the EASD/WHO definition. It is suggested that the Agency clarifies this.	Acknowledged and clarified
Line 881	6	**Comment:** It is critical that ADAs hypo definition now is introduced as it collects more hypos by its higher limits 3.9 mmol/l and thereby is less sensitive to real clinical findings.	The ADA definition is just stated as example. It should be considered that new glucose-lowering agents are developed globally, not just for a specific market.
Line 884	6	**Comment:** Could the Agency specify that the mentioned ADA guideline is the American Diabetes Association Workgroup on Hypoglycaemia. Defining and Reporting Hypoglycaemia in Diabetes, Diabetes Care 2005; 28:1245-1249?	Correct
156-159	6	**Comment:** The guideline recommends the conduct of PK studies in all types of patients in whom treatment is intended, including children. Depending on the PK profile of the investigational drug established in a wide range of adults subjects/patients, in some selected cases the PK in children with type 2 diabetes could be	Not accepted The guideline states that “Population PK approach and PK/PD modelling may be additional tools to achieve this objective.”

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		adequately assessed implementing Modelling & Simulation and could be confirmed with a population PK approach. In addition, the guidance seems to suggest that PK studies have to be conducted in children with type 2 diabetes and not in children, with a similar age and BMI range as patients with type 2 diabetes, but without the disease. **Proposed change (if any):** Consider the addition of the use Modelling & Simulation instead of a dedicated PK study for selected cases when the investigational drug has appropriate PK characteristics established in a wide range of adults. Clarify whether subjects with similar age and BMI range as patients with type 2 diabetes could be acceptable for PK studies.	
Lines 206-209		**Comment:** The guidance mentions that adding an oral investigational product to patients treated with insulin could be clinically meaningful if a decrease in the insulin dose is accompanied by favourable changes in body weight or the incidence of hypoglycaemia in addition to improvement in HbA1c. The study design to assess the addition of an oral agent to patients on insulin will need to focus either on the assessment of improvements in glycemic control which requires the insulin dose to be kept constant as much as possible	Accepted This has been clarified

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		or the assessment of an insulin-sparing effect which will require the insulin dose to be flexible and titrated. In this case an improvement in glycemic control can not be expected. **Proposed change (if any):** Consider deleting “in addition to improvement in HbA1c” (line 209).	
Line 381	6	**Comment:** Many patients who would be candidates for the addition of a new agent to ongoing insulin therapy are not receiving a dose of insulin greater than 0.5 u/kg/day. While clinical inertia may account for some of these patients insulin doses, the failure to up-titrate is frequently (? usually) due to prior issues related to hypoglycaemia, weight gain, patient compliance with multiple injection regimens, or other tolerability issues. The efficacy and safety of a new agent can be adequately assessed in patients who are on lower daily doses of insulin, and indeed this will likely represent a large proportion of patients who would ultimately be prescribed the new agent in combination with insulin. **Proposed change (if any):** Delete the phrase "e.g., ≥ 0.5 U/kg/day"	Accepted
Lines 722-733		**Comment:** It is unclear whether these studies of insulin in children would be required prior to approval of the	It has been clarified that sufficient safety data in adults should be available prior to commencing paediatric studies

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product in adults (as is suggested in the section discussing other antihyperglycemic therapies). **Proposed change (if any): Clarify whether studies of insulin in children will be needed prior to marketing authorization**	
Lines 468-472	8	**Comment:** The age brackets indicated should match those defined in the guideline ICH E7 regarding the geriatric population. **Proposed change (if any):** Replace the following text: “For products associated with hypoglycaemia, a detailed analysis of hypoglycaemic episodes noted in clinical trials should be provided (i.e. analysis stratified for age: ≤ 65 years, > 65 years, >75 years, timing of the episodes in relation to drug exposure, diurnal distribution, and for each episode: time of onset, time after last drug administration, time after meal, severity, duration, outcome of hypoglycaemia, dose of treatment).” With “For products associated with hypoglycaemia, a detailed analysis of hypoglycaemic episodes noted in	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical trials should be provided (i.e. analysis stratified for age: < 65 years, 65-74 years, 75-84 years, ≥ 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)."	
Line 473-475		**Comment:** Refer the need to monitor adverse outcomes resulting from hypoglycaemia consequences, such as dizziness that might lead to falls in the elderly. **Proposed change (if any):** Add to the following text: "Use of continuous glucose monitoring, providing more complete information on night profiles, should be considered especially in patient groups at increased risk for hypoglycaemia." the highlighted part in green: "Use of continuous glucose monitoring, providing more complete information on night profiles, should be considered especially in patient groups at increased risk for hypoglycaemia. Outcomes from hypoglycaemic episodes (such as dizziness) that might contribute to complicated adverse events in the elderly (such as	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		falls) should be closely monitored."	
Lines 630-634		**Comment:** Refer in the Pharmacokinetics for insulin preparations that the studies should also be made in elderly, specifically, with the referred age brackets. **Proposed change (if any):** Add to the text the highlighted part in green: "Apart from the kinetic studies in healthy volunteers, studies should be performed in type 1 and in type 2 diabetic patients, adults, children (stratified by age) and the elderly (stratified by age brackets 65-74 years old, 75-84 years old and ≥ 85 years old), and in various situations associated with PK variability: insulin dose, site of injection and thickness in fat layer contribute to the rather considerable variation in the PK parameters seen with insulin even in the same individual over time."	Not accepted. Considered not to provide relevant additional information for an insulin.
Lines 683-684		**Comment:** Reclassify the elderly patients referred as the approved age brackets by the ICH E7. **Proposed change (if any):** Replace the following text: "A reasonable number of elderly and very elderly patients (>65 years and >75years, respectively)	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		should be included in the therapeutic confirmatory studies." with "A reasonable number of elderly patients (65-74 years, 75-84 years, ≥ 85 years) should be included in the therapeutic confirmatory studies."	
Line 693	9	**Comment:** The basis for the age specific stratification should be included proposed change (if any):	Standard stratification in the paediatric population
Line 738	9	**Comment:** do not use the term "autoimmunogenicity"proposed change (if any): use the term "autoimmunity"	Corrected
Line 737-739	9	**Comment:** it is conceivable that there may be biomarkers other than beta cell specific autoantibodies, therefore, more general terms may be better used here; e.g. primary prevention – or stop initiation of markers of beta cell autoimmunity and secondary prevention – stop progression of disease after markers of beta cell autoimmunity are present. Also it is not islet related autoantibodies but beta cell specific autoantibodies **Proposed change (if any):** see above	Partially accepted. The focus of current drug development is on subjects at high risk for developing type 1 diabetes, which is likely driven by considerations regarding feasibility of clinical trials (to show a relevant effect) and potential safety concerns of investigational drugs. Primary prevention is mentioned in the guideline but does not usually include pharmacotherapy.
Line 742-744	9	**Comment:**	The concerned paragraph has been revised.

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		Should include the concept that within this group defined by antibodies only, there are subgroups with even higher risk. This whole paragraph would be better just stating that current data suggests that measurement of antibodies, insulin secretion, and glucose tolerance can identify groups of individuals with widely variable degree of risk over 5 years; from a low risk of 3-5% to very high risk of >75%. **Proposed change (if any):** see recommendation above "Within the group of at-risk subjects with beta cell specific autoantibodies, there are subgroups with even higher risk that can be identified based on not only measurement of antibodies but insulin secretion and glucose tolerance that can identify groups of individuals with widely variable degree of risk over 5 years; from a low risk of 3-5% to very high risk of >75%."	
Line 742	9	**Comment:** No justification as to why only these antibodies noted. Indeed, measuring just these two will leave out those with more than 2 autoantibodies. Moreover, ICA continues to confer additional risk above the other markers.	Concerned paragraph has been revised to be more general.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): not limit to just what is noted—suggest using comments noted above	
Line 745-746	9	**Comment:** Strongly disagree with this comment because the issues of risk/benefit needs to be taken into account. A 5-10% risk could justify intervention for secondary prevention and a very safe primary prevention approach may have application for universal immunization of the childhood population, which has an overall risk of ~ 0.3% if it proved safe. **Proposed change (if any):** "Pharmacological intervention studies that aim to delay or prevent the onset of T1DM need to consider the overall benefit/risk of the intervention in the target population. "	Relevance of safety profile is stated at the end of the section. There is a serious concern about the long-term use of immunosuppressants/immunomodulators in this condition. Nevertheless, the point is well taken and considered.
Line 746-748	9	**Comment:** Again, missing the whole notion that antibodies alone are only one parameter to define risk. As noted above there are other parameters (insulin secretion, glucose tolerance, BMI, HbA1C changes over time) that when used with autoantibodies give a more precise risk score.	Acknowledged but would like to keep the reflexion of risk factors to a minimum. Section has been revised to be more general
Line 749	9	**Comment:**	Changed to "preferably double-blind"

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		While one favors double blind trials whenever feasible and ethically justifiable, there are situations particularly in prevention in which double blinding may be inappropriate. For example, double blinding anti-CD3 in prevention, which is in trials today, would require children to have two weeks of IV saline. Since, unlike in those with disease there is no possibility of patient or physician altering course of disease, a strong argument can be made on ethical grounds against this approach. **Proposed change (if any):** "Clinical studies should be randomized, double blind and placebo-controlled when feasible and practical based on the intervention"	
Line 749-750	9	**Comment:** If the indication for use of drug is prevention of diabetes, this is reasonable, but it would be useful to have trials with "earlier" endpoints (reversal of dysglycemia, reversal of increasing HbA1c, preservation of C-peptide, prevention of progression to the next substage in the at-risk setting) if only to provide data to support longer studies that show prevention of diabetes. **Proposed change (if any):**	This is beyond the scope of the guideline. The mentioned endpoints and especially their clinical relevance have not been established which would be necessary for a benefit-risk assessment. It will be up to the Applicant for a specific product to properly justify such endpoints. Preservation of beta cell function is addressed in section 6.2

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"The primary efficacy endpoint should be the cumulative diabetes incidence or for earlier stage trials, prevention of progression toward insulin-dependence, as evidenced by reversal of dysglycemia, reversal of increasing HbA1c, preservation of C-peptide, or prevention of progression to the next substage in the at-risk setting."	
Line 750-755	9	**Comment:** This is too narrow and does not take into consideration issues around loss of beta cell function- with change in glucose tolerance, loss of C peptide, etc. **Proposed change (if any):** "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. Other biomarkers that could be monitored include: reversal of dysglycemia, changes in glucose tolerance, reversal of an increasing HbA1c, preservation of beta cell mass- to provide additional evidence of efficacy. Immune markers such as insulin, GAD65, ICA512, ZNT8, and IA-2beta antibodies should be measured at baseline and at predetermined time points during the studies. Genotyping may be important for treatment success."	Accepted
Line 756-759	9	**Comment:**	As indicated, the mentioned "step-down approach" is

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is not clear what the rationale is for these groups. Also, what defines “efficacy” . One will be unable to perform an efficacy study in these separate populations.	recommended for safety reasons. It is not expected to demonstrate a statistically significant effect in every subgroup, although the observed effect size should still be relevant.
Line 758	9	**Comment:** **Proposed change (if any):** “monogenic” not “monogenetic”	Accepted
Line 763	9	Comment: What does “rather benign” mean. These sentences need to be better stated along lines of risk/benefit	This sentence should make clear that interventions with serious risks would most likely not outweigh potential benefits in this indication.
Line 778	9	**Comment:** No one knows that the figure is 10-20% or that this is end-stage insulitis	It is said that this is an estimate
Line 780-783	9	**Comment:** The comment “be initiated as soon as possible after manifestation of the disease to have a chance of showing a meaningful benefit” is not necessarily true. We have learned that there is commonly the presence of beta cell function at further times from diagnosis, which if preserved may prove clinically meaningful. Ideally the earlier the better but do not rule out opportunities for later interventions in the first 12 months after diagnosis that may prove clinically meaningful.	The wording has been softened but demonstration of a clinical benefit will be much more likely in patients with recent onset of diabetes.
Line 785	9	**Comment:**	Considered to be clear

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		What does this mean?: “at least for a certain time”	
Line 789	9	**Comment:** Again, the data supporting the statement “within 3 months” is weak and the time frame should be relaxed until there is good data. It may prove possible to preserve residual C-peptide throughout the first year or even later after diagnosis. There also may be significant non-functional residual beta cell mass, reflecting stressed beta cells, that is not detected in a mixed meal tolerance test that may be recoverable with specific interventions.	See comment above
Line 790-794	9	**Comment:** Change from baseline may not be the best outcome measure. Indeed, it is possibly more likely to demonstrate clinical benefit if outcome is above a particular C-peptide level rather than a change from baseline. Change from baseline may address drug efficacy, but not clinical efficacy. Both should be considered.	Could be included as secondary endpoint.
Line 793	9	**Comment:** Hypoglycemic episodes will be too rare to prove meaningful as a primary endpoint.	Several clinically relevant and thus acceptable endpoints are mentioned, hypoglycaemia being only one of them.
Line 794	9	**Comment:** It is not a good idea to include “not requiring insulin therapy”. This is very dependent on non-random factors and would require very large trial to prove	Several clinically relevant and thus acceptable endpoints are mentioned, insulin-independence being only one of them.

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		convincingly. Should not be considered as a primary endpoint.	
Line 796	9	**Comment:** What is basis for the statement: Other secondary endpoints should include fasting and postprandial blood glucose concentrations, --no good data to support	Considered supportive data. Standard measurements in diabetic patients.
Line 797-798	9	**Comment:** The statement "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 vague what is meant by treatment benefit. This is not clear. Must it be primary endpoint or would secondary endpoints suffice? We would argue that attaining secondary endpoints at two years and ideally longer may be clinically meaningful and impactful – e.g. decreased insulin dose requirements or improved glucose control- e.g. decreased glycemic variability. Also see comments above about what should be considered as primary endpoints.	The chosen primary endpoints (preferably supported by the secondary endpoints) should indicate maintenance of effect over at least 2 years. It is not necessarily expected that this effect is still statistically significant at that time (e.g. due to drop-out of patients from the study). In the end, the relevance of the observed effect will be weighed against the identified and potential safety issues.
Line 866	9	**Comment:** Pediatric OGTT dosing not included 1.75 grams/kg to maximum dose of 75 grams glucose	Included in section 7.1 'Diabetes definition'
904	2	The definitions for "hypoglycaemia" now align with the FDA guidance. However, it should be noted that there is currently no separate definition of "severe	Clarified in the guideline. There is no consistent or agreed upon numerical definition of hypoglycemia for the child with diabetes. Nevertheless, BG

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		hypoglycaemic in children" within the FDA framework and therefore the implications of the introduction of this definition for Europe only should be carefully considered by the Agency.	values below 3.3–3.9 mmol/L (60–70 mg/dL) are generally agreed to place the individual at risk for severe hypoglycemia because BG values in this range are associated with alterations in the counterregulatory hormones essential to the spontaneous reversal of hypoglycemia. For clinical use, the value of <3.6 mmol/L (65 mg/dL) has been most often used as the level for defining hypoglycemia in the pediatric population. However, a recent ADA Working Group report suggested using 3.9 mmol/L (70 mg/dL) as the definition in all age groups for research purposes in evaluating therapies designed to alter frequency of hypoglycemia (21). The ISPAD definition has been included in the guideline as an example for definition of hypoglycaemia in children. (Clarke W. ISPAD Clinical Practice Consensus Guidelines 2009 Compendium - Assessment and management of hypoglycaemia in children and adolescents with diabetes. Ped Diabetes 2009, 10:134-45; CRYER PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. N Engl J Med 2004: 350: 2272–2279 (Review); WORKGROUP ON HYPOGLYCEMIA ADA. Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. Diabetes Care 2005: 28: 1245–1249 (Review)
523	2	The text states "Central adjudication for adverse	Clarified.

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		events of interest. " Further clarification should be included as to the definition of "adverse events of interest". Confirmation should be provided on whether this would be anticipated to be an adjudication for presence/absence of a diagnosis or to determine causality and relationship to study drug. Text should also be included to state that non CV adverse events of interest could be considered for potential adjudication, as appropriate, depending on the AE.	Adverse events of interest should be chosen based on the known safety of the product class, the mechanism of action of the investigational drug and/or the non-clinical findings.
Line 526-538	6	**Comment:** How extensive should collection of baseline data be, especially for CHF (would e.g. NYHA classification be considered sufficient)?	Reporting of NYHA class would be sufficient
Lines 526-538	6 + 7	**Comment:** The guidance recommends that the study population should mimic the target population as much as possible. However, the guidance also recognizes that an increased number of patients with increased cardiovascular risk will need to be included to assess the cardiovascular safety of an investigational drug. It would be very challenging to accrue the required number of cardiovascular events in a population that mimics the target population (e.g. the prevalence of prior non-fatal CV events in type 2 diabetes is only about 25-30% based on the literature). **Proposed change (if any):**	Not accepted Previously, patients with high CV risk were systematically excluded from most clinical developments. The new guideline stresses that such patients are an important part of the diabetes population and should thus be represented in the study population, however, without mentioning a specific number or percentage.

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		Consider to clarify that the study population should have an average cardiovascular risk that allows the assessment of the cardiovascular safety of the investigational drug.	
Line 577	6	**Comment:** It is stated that “A summary of what is known about CV risk should be proposed for the SmPC”. It is thus suggested to add a template text for the SmPC.	Not accepted. SmPC templates change over time and are available on the EMA homepage
Line 693	6	**Comment:** The overall incidence in children <1 year is too low to recruit an adequate number of subjects. In case of subjects < 1 year it is difficult to diagnose type 1 diabetes mellitus and strict stratification is not realistic. Furthermore in paediatric patients < 1 yr with diabetes often have a form of the disease pathogenetically and clinically different from type 1 DM. The <1 year group is therefore not possible to do especially as placebo requirement exist as well. As a result waivers are generally issued for the investigation of insulin preparations in patients < 1. This should be reflected in the guideline. Also management of hyperglycaemia in the vary young age group < 2 is extremely challenging due to intricate insulin dosing requirements (e.g., small doses that may require diluted insulin), variable feeding patterns and the need to train parents on appropriate	The difficulties are acknowledged. However, at least some data (i.e. some clinical experience with the test agent) are expected in very young children. Placebo-control would be unethical in insulin-dependent patients and is thus not required.

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		care. Given the low number of cases as well as the critical status and special management considerations for neonates and infants with diabetes, including these patients in a type 1 diabetes clinical trial would be unsuitable. It should be a 2-6 year as the lowest and then modelling can take place to those below 2 years. Please allow for a different approach regarding children below 1 and 2 years. **Proposed change (if any):** It is recommended that trials be performed in patients 2 to < 18 yr old. The need for studies in patients below 2 years, should be considered and paediatric patients should be stratified by age group: < 1 year, 1 to < 2, 2 to < 6y, 6 to < 12y, 12 to < 18y.	
Line 702	6	**Comment:** To require continuous blood glucose monitoring in children below 2 years is not reasonable If continuous glucose monitoring is used, could the Agency clarify what variable would be considered in evaluation of hypoglycemia? A composite of symptomatic episodes and confirmed low continuous glucose monitoring excursions? **Proposed change (if any):**	It is acknowledged that CBG monitoring may be difficult in young children. However, recognizing hypoglycaemia in young children may be challenging. Various signs and symptoms including autonomic, cognitive, behavioral and non-specific signs and symptoms are possible. A suspicion of hypoglycaemia should preferable be confirmed by blood glucose measurement.

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		Suggest that the wording is changed to: The use of continuous blood glucose monitoring may provide additional information.	Accepted with the addition “relevant” information.
Lines 224-226	7	**Comment:** The guidance requests that any claims regarding improvement of cardiovascular risk be based on data that show a benefit beyond the effect of improved glucose control. Although there is general agreement that glycemic control has potentially a small beneficial effect on cardiovascular risk avoiding any difference in glucose control would only be possible in active-controlled studies or patients with very low HbA1c at baseline. A comparison of the investigational agent with standard of care will result in a difference in glycemic control in the initial 2-4 months of the study. There is no evidence that such a relatively short duration and small magnitude of a HbA1c difference affect cardiovascular risk. Therefore superiority claims based on results from such studies should be considered evidence of cardiovascular benefit compared to a standard of care. **Proposed change (if any):** Consider adding clarification that a difference in glycemic control over a short period could be	Section 4.1.5 talks about cardiovascular risk factors (e.g. hyper lipidemia). Assessment of cardiovascular risk is addressed in section 4.4.3 ‘ Long-term safety and cardiovascular safety’.

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		acceptable to evaluate cardiovascular risk.	
Lines 246-247	7	**Comment:** While it is acknowledged that patients with high A1C levels will likely be more hyperglycaemic and would require immediate initiation of antihyperglycemic therapy, the specification of an upper limit of A1C of 8.5% for placebo-controlled monotherapy studies is unnecessarily restrictive. First, in the absence of symptomatic hyperglycemia, the deleterious effect of short-term hyperglycemia in patients with type 2 diabetes has not been established, and it is well-established that the chronic complications of diabetes take years to develop in the context of hyperglycemia. Secondly, study design elements which protect patients against prolonged periods of severe and clinically meaningful hyperglycemia should be considered the primary method for ensuring patient safety and ethical study conduct. Third, there is value to assess the efficacy and safety of the investigational drug in patients with a wide range of hyperglycemia. **Proposed change (if any):** Delete the parenthetical phrase (e.g., less than 8.5%), and assess the A1C entry criteria on the basis of the specific study design elements (e.g., study duration, glycemic rescue thresholds, population, etc).	Not accepted. Similar comments as received from stakeholder 2. See response above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 379-391	10	**Comment:** The primary objective of the study should be to demonstrate a greater reduction of the insulin dose under the combination of insulin with “drug” vs. the combination of insulin plus placebo. For this purpose, the doses of “drug” and placebo must remain stable. The dose of insulin should be variable and adapted to reach and maintain a defined level (or range) of A1c. At least for the patients in the placebo arm, the proposal to freeze the insulin dose for study purposes in those with unsatisfactory glycaemic control and to treat them with placebo is questionable. **Proposed change (if any):** Omit proposal to keep insulin dose stable.	The guideline provides recommendations regarding combination studies with insulin. Other study designs are possible but in such cases EMA scientific advice is recommended.