22 June 2023
EMA/279883/2023
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. 2)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation in 2018 and the reflection paper as released for consultation in 2022.

Stakeholder no.	Name of organisation or individual
1	EFPIA
2	IMI Rhapsody
3	JDRF International
4	T1D Outcomes Program Steering Committee
5	The diaTribe Foundation
6	Profil institute for Metabolic Research
7	Boehringer Ingelheim
8	AstraZeneca
9	Prescrire
10	European Association for the Study of Diabetes e.V. (EASD)

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

1. General comments on the draft document as released for consultation in 2018– Overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	EFPIA welcomes the opportunity to provide input to the "Draft guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus – CPMP/EWP/1080/00 Rev. 2"	
1	EFPIA supports the use of real-world evidence data. It is suggested that the scope of the guidance be extended from pre-marketing authorisation clinical development to include guidance on the use of real-world data such as obtained via observational studies and other sources.	Please refer to the areas that have been updated (see concept paper). There is currently no intention to expand the guideline to include post marketing requirements.
1	EFPIA welcomes the inclusion of the **estimands** concepts in the document. In order to provide additional clarity regarding the targeted treatment effect, it would be beneficial to either use the framework as laid out in the draft ICH E9 addendum and/or explain further in a summary statement what the targeted treatment effect (estimand) is (for example): o To include the impact of non-adherence to treatment in the treatment effect estimate, o but not to include the potential positive impact of the effect of rescue medication in the treatment effect estimate. Moreover, it would be helpful to describe which strategies are considered appropriate for handling various reasons for discontinuation of treatment. Most diabetic patients who discontinue treatment due to adverse events or any other reason will need to be switched to another anti-diabetic medication after discontinuation of trial product. Consequently, the data collected after discontinuation of trial product will reflect the effect of the new treatment.	This section has been updated to increase clarity

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	In addition, there are some statements made about modelling of data in Section 4.2.2.1. The current wording is a mixture between discontinuation of treatment and introduction of rescue medication. Also, reference is made to data from a placebo arm, when development programmes will include active comparator trials. It is suggested that modelling of the effect after initiation of rescue medication is based on data obtained in the placebo group in a scenario where medication was not introduced. Does the agency have a recommendation to the approach in active controlled trials where no placebo group is included? Finally, it may be beneficial to state that modelling approaches should reflect that the start of rescue medication can be indicative of a decline in the patient's health, lack of efficacy of the product or that the patient is not compliant and that this would be reflected as such in the analysis. It may be beneficial to include an additional statistics section in the document, which provides a description of points to consider when designing analysis plans, and to follow the same structure and level of detail taken in the Guideline on the clinical investigation of medicines for the treatment of Alzheimer's disease (CPCM/EWP/553/95 Rev. 2 – section 11) Please see other comments on Estimands in section specific comments on the text.	
1	EFPIA welcomes the recognition that beneficial effects on long term complications (micro- and /or macrovascular complications): - are not a mandatory requirement for the approval of a new medicinal product - can be reflected in the product information (SmPC section 5.1) as stated in **Section 4.2.4. Effect on long term complications**. Reductions in HbA_{1C} levels are known to prevent microvascular complications as mentioned in lines 190-191. As such, it is not clear why a *"first line unrestricted monotherapy indication" (lines 265-266) would require a long term controlled trial to a clinical endpoint rather than the control of HbA_{1C} (see lines 384-385): "In addition,*	Requirements for monotherapy indication have been updated, but effect on diabetes complications is not expected to be included in section 4.1.

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	beneficial effects on micro and/or macrovascular endpoints and a well characterized safety profile (including data on long term safety) should be documented before a first line monotherapy indication would be considered approvable." In addition, this requirement would increase the duration and sample size of the clinical trial to the point where patient's access to new product innovation would be harmed. It may be more appropriate to require confirmation as a post-marketing requirement. In addition EFPIA would like to underline those beneficial effects on micro and/or macrovascular complications deserve a more prominent place in the labelling than just documentation in SmPC section 5.1 as a pharmacodynamic characteristic of a medicinal product. This would be in line with the approach recently taken for PCSK9 inhibitor (evolocumab, Repatha) where CV outcome data from a Ph3 CV outcome study (Fourier) has served as the basis for updating the indication section. Source: Repatha EPAR, 2018 Many products treat diabetes, but beneficial effects on complications have not been investigated and/or demonstrated for all products. It is important that prescribers know which products can reduce the risk of cardiovascular complications and other serious complications. The importance is acknowledged in lines 173-177 of the guideline: "*Treatment of patients with type 2 diabetes should be based on a holistic approach in order to improve blood glucose levels and reduce the risk of both micro- and macrovascular complications. Even though the primary aim of the confirmatory studies with the glucose lowering agent is to demonstrate a favorable effect on blood glucose control, it is also important to consider effects of the test agent on other CV risk factors*." **Proposed change:** Beneficial effects of the drug on development of these complications in the intended target population can only be evaluated properly in large scale and long term controlled clinical trials and are not a mandatory requirement for the approval of a new medicinal	

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	product. ~~**but may be needed for a first line unrestricted monotherapy indication (see 4.4.4)**~~ in line 262-265. If beneficial effects on micro and/or macrovascular complications have been documented in (parts of) the target population, such data may be included in the product information (SmPC sections **4.1 and** 5.1). This would reflect that the treatment, in addition to improving glycaemic control, also has a documented effect on long term complications, both being part of the concept of ”treatment of diabetes” in line 267-268.	
1	EFPIA welcomes the inclusion of the patient reported outcomes (PROs) in the document **in section 4.2.5.** The use of disease-specific patient, clinician, and observer-reported outcomes for diabetes is recommended as it may reveal important information on how treatment affects patient experience and health-related quality of life. Suggest to clarify that this section relates to patient, physician and parent related outcome. PROs are not only relevant to contextualize observed effects on measures derived from CGM monitoring and suggest to delete the sentence "Furthermore, such information will help to …… normal range" in line 273-275. **Proposed change: (line 272 + 273-275)** Suggest to add "clinician reported outcome and observer reported outcome" to text in line 272, and to delete "Furthermore, such information will help to …… normal range" in line 273-275.	Sections are considered to be clear enough
1	EFPIA supports the definitions of hypoglycaemia to be standardized and welcomes the inclusion of the new standardized classification published by the International Hypoglycaemia Study Group referred to for hypoglycaemia in adults (**Definitions, Hypoglycaemia**, line 877). The advent of more widespread use of continuous glucose monitoring (CGM) and other diabetes technologies has led to other consensus groups	The definitions have been updated according to recent recommendations

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	addressing the need to have a common approach to the definition of glycaemic metrics including hypoglycaemia. The new classification published by IHSG is also supported by Learned Societies such as EASD, ADA, AACE, JDRF and ISPAD. The text defining the three levels of hypoglycaemia in the revised guideline is recommended by EFPIA to be aligned with the wording used in the publications from EASD, ADA, AACE, ATTD and JDRF i.e.: **Severe hypoglycaemia:** Based on the above references the text in line 883 is proposed to be changed to: **Severe hypoglycaemia (level 3)** **Clinically important hypoglycaemia:** Based on the above references the text in line 889 is proposed to be changed to: **Clinically significant hypoglycaemia (level 2)** **Glucose alert value:** Based on the above references the text in lines 892-893 is proposed to be changed to: **Hypoglycaemia alert value (level 1)** A glucose value less than 3.9 mmol/l (70 mg/dl) and above or equal to 3.0 mmol/l (54 mg/dl). The relevant references to be mentioned are: - International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-7 - American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes-2018. Diabetes Care. 2018;41(Suppl 1):S55-S64. - Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, Maahs DM. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatric Diabetes 2018; https://doi.org/10.1111/pedi.12698	

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	- Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, et al. Standardizing Clinically Meaningful Outcome Measures Beyond HbA_{1c} for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. Diabetes Care. 2017;40(12):1622-30 - Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care. 2017;40(12):1631-40. **<u>Hypoglycaemia in children</u>** The ISPAD definition of Hypoglycaemia in children presented in this version of the guideline (**Definitions, Hypoglycaemia**, line 899) is from an old version i.e. ISPAD 2009. The 2018 ISPAD hypoglycaemia guidelines have been harmonized with the IHSG. The relevant reference to be mentioned is: Abraham MB, Jones TW, Naranjo D, Karges B, Oduwole A, Tauschmann M, Maahs DM. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatric Diabetes 2018; https://doi.org/10.1111/pedi.12698 Therefore EFPIA recommends this section on "**Hypoglycaemia in children**" to be updated to reflect ISPAD's 2018 guidelines.	
1	EFPIA welcomes recommendations on **general design elements in section 4.4.4.1** With the increasing use of continuous glucose monitoring in clinical practice and as it can be shown that reduction of glycaemia reduce long-term risk of development of microvascular complications, EFPIA believes that these newer ways of obtaining validated CGM data may justify the use of CGM data as primary endpoint when duly justified.	CHMP is still of the opinion that HbA1c should be the primary endpoint in confirmatory trials.

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	EFPIA therefore suggest to include "If justified, validated CGM data such as time in range and even hypoglycaemia data, could be used as primary endpoint in confirmatory trials." to the paragraph after line 342 (**4.4.4.1. General design elements,** "The primary endpoint should be HbA1c while secondary endpoints should include other measures of glycaemic control …" and also to the paragraph after line 572 in **5. 3.1 Efficacy criteria/Treatment goals/Methods to assess efficacy.**	
1	EFPIA welcomes recommendations on studies to be performed in **children and adolescents with type 2 diabetes mellitus in Section 4.5.2** As the size of the population of children and adolescents with type 2 diabetes is limited and recruitment in several trials have shown to be extremely difficult EFPIA suggests the following text to be added after the recommendation to run separate trials (**Section 4.5.2. Children and adolescents)**: **"Extrapolation of adult data to adolescents and/or younger children may be used if appropriately justified to avoid exposing children to unnecessary clinical trials. This approach could also help address the feasibility issues of the limited paediatric patient population with Type 2 DM (see section 5.5.2).”** as stated in E-11 and in Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA, draft of 9 October 2017).	Partly accepted. The wording has been updated
2	IMI2 RHAPSODY welcomes the opportunity to comment on the above concept paper regarding additional changes to the guideline to be considered, based on recent developments and queries from different stakeholders.	
2	Diabetes is presently classified into two main forms, type 1 and type 2 diabetes, but type 2 diabetes in particular is highly heterogeneous. A refined classification could provide a powerful tool to individualise treatment regimens and identify individuals with increased risk of complications at diagnosis.	Comments acknowledged but not considered to be within the scope of this revision of the guideline.

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	A proposal has been published by Ahlqvist et al. (2018) The Lancet Diabetes & Endocrinology, Vol 6 No 5 361-369. Future therapeutics could be developed for treating these subgroups. It would be useful if the guidance could advise on developing therapies, in novel subgroups of adult-onset diabetes. IMI2 RHAPSODY is gathering data which may help in the refinement of this classification.	
2	An area for future guidance within the revision concerns the qualification of biomarkers and biomarker panels, specifically concerning patient selection strategies, clinical endpoints, and clinical trial designs for prediabetes and diabetes disease prevention and management. Type 2 diabetes (T2D) is a disease where precision medicine has the potential to add considerable value. Choice of therapy, for example, might be informed using panels of biomarkers to determine the likelihood that a patient will respond adequately, or the risk of side-effects, disease progression, or for dose optimization. Although the guidance may not be able to provide specific recommendations at this time for this type of strategy, some consideration of therapeutic development in the future would be useful.	Not accepted. This is seen as too premature to include in the guideline at this point in time.
2	Having the ability to identify (using biomarkers) patients who will progress from prediabetes to T2D would allow for the development of appropriate treatment options. There is an absence of a definition of prediabetes in the guidance, line 809 mentions "the prediabetic state", however line 854 Definitions does not include a definition of the pre-diabetic state. This is needed and could include a more clinically useful definition of prediabetes than a 'static' definition. For example, a dynamic definition, whereby changes in body weight and glycaemia, alongside other biomarker changes, such as insulin and c-peptide, during a defined period are used to stratify populations. Such a dynamic definition may improve the classification of at-risk individuals. If therapeutic products are being developed to delay the onset of T2DM, without a patient selection	Not accepted. This is seen as too premature to include in the guideline at this point in time.

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	criteria (ie prediabetic classification), it essentially means that the treated population would be prophylaxis of the general population.	
2	The scope of the guidance listed in line 110, is the clinical development programmes intended to support the registration of new medicinal products for the treatment of diabetes mellitus. However, it would seem important to provide guidance not only for registration, but for slightly further on into the life cycle of medicinal products for the treatment of diabetes mellitus. For T2D, it could be worthwhile including guidance on the use of observational data and their role in evidence generation, particularly in the post-approval setting. Advanced epidemiologic, (bio-) statistical, and simulation modelling techniques can be applied to observational, as well as experimental data, to identify worthwhile innovation routes. While RCTs may provide the ultimate evidence, in precision medicine, appropriate analysis of observational data is almost as essential. (ref: IMI GetREal http://www.imi-getreal.eu/About-GetReal/Overall-objectives).	Not accepted. Post approval phase is not within the scope of this guideline.
3	JDRF is the leading global organization funding type 1 diabetes (T1D) research with more than 100 U.S. locations and six international affiliates. Our mission is to accelerate life-changing breakthroughs to cure, prevent and treat T1D and its complications and we collaborate with a wide spectrum of partners in the community to achieve this mission. Founded in 1970 by parents of children with T1D, JDRF has invested nearly $2 billion in research since its inception and employs over 20 scientists to manage its research portfolio. JDRF is pleased that the EMA has proposed revisions to the guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus. JDRF's detailed comments are provided below.	
4	In December 2015, the Type 1 Diabetes (T1D) Outcomes Program, a multi-disciplinary program including representatives of all T1D stakeholders, was launched to better define the important outcome measures for T1D beyond HbA1c. The Steering Committee of the	

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	T1D Outcomes Program was made up of representatives from the leading diabetes clinician organizations and research funders, including the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF, The Leona M. and Harry B. Helmsley Charitable Trust, the Paediatric Endocrine Society, and the T1D Exchange. The T1D Outcomes Program developed consensus definitions for a set of priority outcomes for T1D which was published[1] in Diabetes Care in November 2017. Consensus definitions were reached for the following outcomes: hypoglycaemia, hyperglycaemia, time-in-range, and diabetic ketoacidosis (DKA). The T1D Outcomes Steering Committee is providing comments on the revision to the diabetes guideline based on our consensus on diabetes outcomes beyond HbA1c. One of the goals of the program is to have these outcomes adopted and utilized by regulators in their decision making. Our detailed comments follow.	
5	The diaTribe Foundation is pleased to submit public comments on the EMA's recently published revised draft guidance on the clinical investigation of medicinal products in treating or preventing diabetes. We are excited to see EMA's leadership in this area, particularly in ensuring that patients can more easily assume diabetes management. We would like patients as well as doctors, nurses, and healthcare systems to succeed, and we are grateful for your work on this front. We are especially pleased to see further focus on defining hypoglycaemia, and we appreciate the chance for patients to use more therapies that will improve short-term results and minimize the chances of complications down the road. The diaTribe Foundation was created to improve the lives of people with diabetes, prediabetes, and obesity, and to advocate for action. Its online resource, *diaTribe*,	

[1] Diabetes Care 2017 Dec; 40(12): 1622-1630. https://doi.org/10.2337/dc17-1624

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	provides content that helps people touched by diabetes live healthier, happier, and more hopeful lives. This draft guidance is a positive step, and we believe it will be a valuable model for the global regulatory community. Nations like the United States, which has not updated its guidelines since 2008, will find this document particularly instructive. The diaTribe Foundation has comments below on the six major revisions proposed for EMA's approach to diabetes therapies. The comments are organized in the following categories: CV safety; outcomes beyond A1C; definitions of hypoglycaemia; adjunct oral treatments for type 1 diabetes; study design/endpoints for delay/prevention of type 2 diabetes; and safety issues associated with high-strength and fixed-combination insulin products.	
5	**CV safety:** We were encouraged to see alignment on proposed pre-approval CV safety requirements between these draft guidance recommendations and the FDA's 2008 CVOT guidance. We are pleased to see greater standardization of CVOT design. We agree that there is great value in measures that standardize how CVOTs are designed and conducted so that the results can be compared to a greater extent across trials, both within and across therapy classes. The draft guidance says that three-point MACE is the "preferred" primary outcome in assessing CV safety, and it suggests that definitions of each component (MI, stroke, CV death) should be "homogenous" across all studies. We recommend consideration of using perhaps even stronger language in an attempt to standardize CVOTs, which may make them more meaningful for HCPs. While the proposed guidelines stipulate that an assessment of CV safety can be embedded in a trial powered to show CV superiority, the EMA has emphasized that this document is focused solely on CV safety and not potential CV benefit of therapies. We recommend that regulators consider formalizing guidance for CV superiority trials. Many patients/providers want more than A1C-lowering. We believe it is important for patients who want cardio- and renal protection, less hypoglycaemia, weight loss, and other key	Comment acknowledged. However, the guideline does not include details about the design of CVOT.

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	benefits beyond-A1C (more on this below). Well-designed and more standardized studies, powered to show significant cardio-protection, will be vital in the outcomes beyond A1C movement and, more generally, in the advancement of diabetes care.	
5	**Outcomes Beyond A1C:** The revised EU guidance says that A1C should be the "appropriate primary endpoint to support a claim based on glycemic control," and it also endorses Patient Reported Outcomes (PROs) and expresses excitement for CGM. We were encouraged to see the draft guidance recommend PROs to reveal "important information on how a treatment affects quality-of-life" and to provide context to CGM-based metrics (glycemic variability, glucose excursions, time in range). Discussed outcomes include treatment burden and impact on daily life, diabetes management, compliance, and cognition. The draft guidance also mentions that questionnaires or scales be validated in diabetes. EMA has already incorporated a PRO on the label for Lilly's GLP-1 agonist Trulicity, detailing improved total treatment satisfaction versus lower perceived hypoglycaemia and hyperglycemia versus exenatide twice daily. *We recommend EMA provides guidance on what the ideal PROs and instruments are, and we are pleased to see the acknowledgement that they will be considered in approval decisions.* CGM is referenced seven times in the text, which recommends its use: (i) when the agent or patient group under investigation has high hypoglycaemia risk (especially nocturnal); (ii) more generally, to assess glucose variability, nocturnal hypoglycaemia, and post-prandial hyperglycemia; and (iii) in pediatrics, where it is described as "preferable" (to SMBG). We were encouraged that the draft guidance is extremely positive regarding CGM for tracking glucose variability, glucose excursions, and time in range, and it doesn't once caution that accuracy may be lacking relative to SMBG. In other countries like the U.S., caution is exercised given somewhat less accuracy in CGM – but from our view, having "arrows" is a very good tradeoff (Pettus J, Edelman SV. Use of Glucose Rate of Change Arrows to Adjust Insulin Therapy Among Individuals with Type 1	It was found complicated to identify ideal PROs so the chosen instrument has to be justified by the Applicant

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	Diabetes Who Use Continuous Glucose Monitoring. Diabetes Technology & Therapeutics. 2016;18(Suppl 2):S2-34-S2-42. doi:10.1089/dia.2015.0369). We also recognize that other things that threaten accuracy, including carb counting and hand washing.	
5	**Definitions of Hypoglycaemia:** We are pleased to see the EMA's inclusion of thresholds and nomenclature that reflect recent hypoglycaemia consensus statements from ATTD and JDRF; those statements confirmed the consensus statements decided last year at ADA: <54 and <70 mg/dl. The document reasons that "there are no clinically important reasons to distinguish between mild and moderate hypoglycaemia, and younger children will almost always need to be treated by a parent or caregiver. Therefore, mild and moderate hypoglycaemia are considered together." *We recommend consideration of whether separate hypoglycaemia definitions for children (e.g., ISPAD is less than or equal to 70 mg/dl) would be useful. Additionally, we recommend all cutoffs should be consistent (i.e., <70 md/dl for IHSG vs. ≤70 md/dl for ISPAD).*	Definitions for children are included in Section8.
5	**Oral adjunct treatments for type 1:** The current EMA guidelines contain no advice on developing/evaluating oral adjunct treatments for type 1 diabetes, and a relevant section is added (#6) in the proposed revision. We approve of the inclusion of consideration for the oral adjunct treatments for type 1, with an emphasis on reducing hypoglycaemia and hyperglycemia and encouraging greater time in zone. Change in total daily insulin dose is not recommended as a central endpoint, which falls in line with commentary from Dr. Chantal Mathieu at EASD 2017. While insulin is complicated to titrate, and while lower doses do impute meaningful benefits to the patient (especially in less weight gain and less likelihood of hypoglycaemia), Dr. Mathieu said that insulin plays a key physiological role. We agree with Dr. Mathieu's recommendation that lowering insulin dose, independent of reducing hypoglycaemia risk, should not be a goal of adjunct treatment, and the proposed EMA guidelines reflect this view. We appreciate the emphasis on minimizing hypoglycaemia through adjunct	A sentence on documenting time-in-range has been added.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	therapy. *We'd recommend that EMA encourage the use of CGM in these clinical trials to calculate time-in-range, as we imagine this will be the most important quality-of-life benefit for type 1 patients.* Section 6 of the draft guidance highlights DKA risk associated with SGLT use in type 1 diabetes. The EMA proposed guidelines are relatively neutral, noting that DKA is a known complication of a dropping insulin dose and requesting that DKA episodes be closely monitored and recorded throughout the clinical program for an oral adjunct drug. We hope that higher DKA rates don't overshadow the tremendous benefits seen with sotagliflozin and current SGLT-2s for type 1 patients because our sense is that that with these therapies approved for type 2, some use is inevitable in type 1, and safety should be prioritized. Our belief is that patients will (continue to) take these agents off-label, and EMA has a valuable opportunity in this revision process to standardize DKA data collection and to promote stronger patient education around DKA.	
5	**Study design/endpoints for delay/prevention of type 2 diabetes:** EMA's draft guidance regarding studies of medications for the prevention/delay of type 2 diabetes is identical to that in the current version, only adding that it should "be recognized that IFG/IGT and type 2 diabetes are different stages of the same disease continuum and that treatment of such subjects could be considered as an initiation of treatment in an earlier stage of the disease rather than preventing the disease." The additional line in the draft guidance seems to create a possible indication for "treatment of prediabetes," though it is unclear how a trial would change for a "treatment of prediabetes" label versus an indication for "prevention of type 2 diabetes." We are glad to see this update and look forward to what degree it will incentivize companies to come to EMA with applications for prediabetes indications. The draft guidance for prevention/delay is rather stringent, calling for RCTs of "substantial size and duration" in high-risk populations and with a "rather benign" safety profile (see table below). Another factor elevating developmental risk and cost is that it's	The new sentence should not be seen as an opening for treatment of prediabetes. It rather reflects the difficulties in finding an adequate population for studying " prevention of type 2 diabetes".

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	still not clear at what point delayed onset of type 2 diabetes is clinically significant, and until it is, EMA is also asking for evidence of CV benefit.	
5	**Safety issues associated with high-strength and fixed-combination insulin products:** With the growing acceptance of higher-concentration insulins (>100 units/ml) and of fixed-ratio combinations containing insulin (namely, basal insulin/GLP-1s), new material is proposed to address safety issues specific to these products. It is clear there is concern over possible medication errors – for example, taking too much insulin when switching from Sanofi's Lantus (glargine U100) to Toujeo (glargine U300). To this end, the draft guidance stipulates that high-concentration insulins and fixed-ratio combinations should only be available in pre-filled pens, minimizing the numerical dosing/titration burden on patients. "No dose conversion or re-calculation should be required when switching between standard strength and higher strength or fixed combination insulin products within the same product range." For fixed-ratio combos, the draft guidance requires that dose steps on the pre-filled pen reflect the units of insulin being injected. *While manufacturers have already been proactive in helping patients/HCPs avoid medication errors with advanced insulins and fixed-ratio combinations, this draft guidance is another push in a most valuable direction. We recommend that drug manufacturers continue to consider the impact of the device side of their products, especially those containing insulin.*	Acknowledged but not within the scope of the guideline

2. Specific comments on text of the draft document as released for consultation in 2018

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 89-90	1	**Comment:** Non-insulin new therapies that in addition to insulin, may improve glycaemic control and/or reduce the risk of hypoglycaemia are being developed for the treatment of type 1 diabetes. Therefore, it is suggested to modify the existing sentence as follows **Proposed change:** " …to be achieved by optimal insulin replacement therapy, **by addition of non-insulin glucose lowering therapies in some patients,** extensive education…"	Not accepted since this is not approved for all patients with type 1 diabetes.
Lines 104-105	1	**Comment:** Cardiovascular risk reduction demonstrated in CVOT trials with glucose lowering medicinal products for the treatment of type 2 Diabetes mellitus has been reflected in the SmPC. **Proposed change:** "…**the reduction of** ~~macrovascular~~ risk ~~reduction~~ **for macrovascular complications** is less certain. **However, recent CVOT trials have demonstrated CV benefit with some glucose lowering medicinal products for the treatment of type 2 Diabetes mellitus.**	Accepted
Line 109	1	**Comment:** Section 2. Scope: Please clarify if ATMP (advanced therapy medicinal products) such as e.g. stem cell therapy are in scope for this guideline.	Not within the scope

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 121	1	**Comment:** Addendum to ICH-E9 on estimands may be referenced to in the text. **Proposed change:** Add in the '3. Legal basis and relevant guidelines' the Addendum to ICH-E9 on estimands. Add references to the Addendum on lines 183-185, 202-204 & 206-210.	Accepted
Line 167	1	**Comment:** Patients with diabetes who have previously failed to achieve glycaemic control on diet and exercise or have not required intensification while being treated with oral glucose lowering agents and not necessarily at an early stage of diabetes are the target population for monotherapy studies. **Proposed change:** "Monotherapy studies are optimally conducted in patients with early stage of diabetes who have previously failed to achieve glycaemic control on diet and exercise or have had a short treatment course with glucose lowering agent **or have not required intensification while being treated with oral glucose lowering agents."**	The paragraph was deleted.
Line 170	1	**Comment:** Usually the diet and lifestyle advice is done as per current practice at each site and it is individualized per patient's needs. No attempt to provide the guidelines centrally. **Proposed change:**	Section has been deleted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Patients enrolled in the trials should be given ~~similar~~ instructions with regard to diet and exercise **according to medical judgement and generally accepted clinical practice.**"	
Lines 176-177	1	**Comment:** In line with the spirit of this paragraph ("holistic approach") the lowering of blood glucose should be evaluated in the context of the evolution of all complications of diabetes – any time this is possible - and not only in the context of the cardiovascular risk factors. **Proposed change:** "…it is also important to consider effects of the test agent on ~~other CV risk factors~~ **the overall risk factors for the development of long-term complications of hyperglycaemia**."	Not accepted. The original text is considered clear enough
Lines 195-208	1	**Comment:** The following sentences in the document can be interpreted as conflicting statements. Line 195 suggest that the treatment effect estimate should target the effect when patients adhere to treatment, however line 206 (at least first part of the sentence) suggests that the treatment effect estimate should reflect the effect of treatment regardless of whether patients adhere or do not adhere to treatment. Suggestion to clarify. **Proposed change:** Line 195 - 'The actual adherence to treatment should be reflected in the target of estimation.' Line 206 – 'Data obtained after discontinuation of treatment are of principle interest for the estimand described above...'	The section on estimands has been updated to increase clarity

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 202-204	1	**Comment**: "According to ICH E9 (R1), only confirmatory trials are in the scope for estimands and the following is stated in lines 191-192 "*…HbA1c is an appropriate primary endpoint to support claim based on glycaemic control*." It is unclear whether the recommendations on the handling intercurrent events apply to other types of trials and other measures of glycaemic control than confirmatory trials with HbA1c as primary endpoint. EFPIA proposes to clarify.	It is clarified that the same strategy can be used for e.g. plasma glucose parameters
Lines 205-210	1	**Comment:** If the missing data were due to taking rescue medication, the values may be missing at random if earlier values were obtained; if the missing data were due to an adverse event, the data may be missing not at random. **Proposed change:** EFPIA proposes adding the following concept to the paragraph: The reason for missing data (e.g. lack of data following study discontinuation or exclusion of post-rescue values) may be used to pose appropriate assumptions regarding the mechanism of missing data.	The section on estimands has been updated to increase clarity
Line 212	1	**Comment:** What is meant by "additional approaches" in line 212, (**Section 4.2.2.1. Haemoglobin A1c**) for non-inferiority trials? Is it "supplemental analyses" according to the draft ICH E9(R1) terminology or "other analytical approaches"? "Supplemental analyses" would allow for other estimands including "new" intercurrent events discovered through important protocol deviations/violations as well as other analytical approaches that target the same primary estimand.	The section on estimands has been updated to increase clarity

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"Other analytical approaches" only allows for other analytical approaches that target the same primary estimand. EFPIA proposed to clarify. **Proposed change (if any):** Suggest writing "supplemental analyses" instead of "additional approaches".	
Line 215	1	**Comment:** Section **4.2.2.1 Haemoglobin A1c** Suggest to state explicitly for the rationale that all intercurrent events are handled with the composite strategy.	The section on estimands has been updated to increase clarity
Line 215	1	The following statement 'The clinical relevance…': may trigger sponsors to develop trial protocols which target an HbA1C value ⩽ 7 and/or 6.5 % in all subjects enrolled. In the aftermath of the ACCORD study, however, clinical treatment guidelines advocate patients must be treated to their own individualized target. Please consider rephrasing this paragraph in order to reflect this and thus avoid protocol dictated intensive treatment in enrolled subjects, who otherwise might have sufficed with a treatment target HbA1c of 8% according to present guidelines. **Proposed change:** The clinical relevance of the observed effect should be further justified ~~by analysing~~ **in another treatment effect of interest assessing** the difference in proportion of patients ……." Add text regarding cut-off levels for elderly and for patients at high risk i.e. individualised targets as indicated in exiting ADA/EASD guideline.	The section on estimands has been updated to increase clarity
Line 215-218	1	**Comment:**	The section on estimands has been updated to increase clarity

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		It is noted that the HbA1c responder endpoint described in lines 215-218 (**Section 4.2.2.1. Haemoglobin A1c**) isn't fully in line with the recommendations provided in the sections above for handling of intercurrent events for evaluation of HbA1c. Generally, it would be preferable to have the same strategies to handle intercurrent events when estimating the effect of treatment across glycaemic parameters including the proportion of patients who reached an absolute HbA1c value of <=7% and/or 6.5% as for the primary haemoglobin A1c endpoint. Therefore, it would be better if the guideline suggests as a primary approach a unified approach to handling of intercurrent events for glycaemic parameters. This statement may be followed with specific guidance on other relevant evaluations including the one currently stated. **Proposed change (if any):** EFPIA suggest adding that a unified approach across glycaemic parameters in handling intercurrent events is recommended.	
Line 217	1	**Comment:** General comment to the text: When "end-of-trial" is mentioned please rephrase to: "end-of-trial (or other predefined time for assessment of endpoint" as done in line 194. unclear "without the use of additional medication" **Proposed change:** "…end-of-trial (or other predefined time for assessment of endpoint without the use of additional medication **(e.g. rescue medication)**" **.**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 219	1	**Comment:** It is not clear how the "without the use of additional medication" plays into this estimand of proportion of subjects the tolerate and benefit long term unless having additional medication is assumed to be lack of benefit. **Proposed change:** Change 'such analyses' to 'This estimate of treatment effect' and add 'without the use of rescue medication'.	The section on estimands has been updated to increase clarity
Line 224	1	**Comment:** Heading in Section 4.2.2.2 only mentions plasma glucose. Given the importance placed on glucose variability (particular time spent out of the ideal glucose range) it is recommended to add other glycaemic endpoint components such as variability in glycaemia (time in range by CGM/FGM, 1.5-anhydroglucitol). Other assessments might also include blood glucose. **Proposed change:** Revised heading to: **4.2.2.2 Plasma glucose and other glycaemic endpoint components** and add to the core text: "In addition to the evaluation of the overall blood glucose control by HbA1c, at least 7-point capillary-blood glucose profiles (before and after each meal, at bedtime and **potentially** during the night) **and other glycaemic endpoint components such as variability in glycaemia (time in range by CGM/FGM, 1.5-anhydroglucitol)."**	Accepted
Lines 227-228	1	**Comment:** EFPIA would welcome the revised guideline to also address the definition of 'Nocturnal hypoglycaemia' which currently varies depending on the	Not agreed. Nocturnal hypoglycaemia is defined as low blood sugar whilst sleeping and

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		sponsor and pharmacological agent. A standardized definition for adults would be of help, as for example "from 00am to 06am" as a suggestion. **Proposed change (if any):** see on comment above a suggestion for definition of 'Nocturnal hypoglycaemia'.	it would therefore be difficult to identify a universal time span.
Lines 237-240	1	**Comment:** Please clarify that the intent of the definition is to include patients who have either received rescue therapy or are withdrawn from treatment due to lack of efficacy as non-responders. **Proposed change (if any):** ...'withdrawn **from treatment** due to lack of efficacy...'	The section on estimands has been updated to increase clarity
Line 241	1	**Comment:** Do not quite understand why this section **4.2.2.3 Insulin parameters** only covers reduction in the need of insulin - could as well be reduction in other antidiabetic drugs (OADs) or drugs used for treatment of complications - e.g. less need for lipid lowering treatment. **Proposed change:** Suggest to add new subsection "**4.2.2.4 Lipid parameters**".	Lipid parameters is covered by section 4.2.3
Line 249	1	**Comment:** The sentence "Patients with a meaningful increase in concomitant treatment of use of rescue medication would be classified as non-responders." This sentence is not only relevant to section 4.2.2.3. and suggest to include this in section 4.2.2.1 as well or move it to the introduction section 4.2.2.	The sentence was deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Suggest to include this in section 4.2.2.1 as well or move it to the introduction section 4.2.2.	
Line 255	1	**Comment:** "A new glucose-lowering agent should preferably show a neutral or beneficial effect on such parameters associated with cardiovascular risk.": The reference "such" is to other CVD risk factors such as LDL and BP. Whereas these are classical risk factors used in clinical practise, other novel biomarkers that serve as proxies for risk, differentiates risk, or represent true pathophysiological markers may also be added to better represent the forefront of clinical science aiming at precision medicine. **Proposed change:** Suggest "novel pathophysiological or risk stratifying biomarkers" be added in text in 252-254.	Partly accepted. Some changes were introduced to this section.
Lines 273-275	1	**Comment:** With regards to the new recommendation on the use of PROs, it is suggested to use of a broader, more encompassing terminology regarding the contextualization of the observed effects on measures from continuous glucose monitoring. A suggestion for the text revision is provided below. **Proposed change (if any):** "Furthermore, such information will help to **contextualize** ~~observed effects on~~ measures derived **parameters characterizing glycaemic control and**	Not accepted. Current text satisfactory enough

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		safety measures derived from continuous glucose monitoring such as glucose variability, glucose excursions and time spent in normal range."	
Lines 283-284	1	**Comment:** Please confirm if "*capillary glucose*" measurements refer to SMPG measurements.	Could be self measured or measured by health care provider
Line 286	1	**Comment:** The text regarding the use of CGM states: "Currently these methods still require traditional blood glucose measurements for calibration…". Some of the recently approved devices for continuous glucose measurement/flash glucose monitoring such as Abbott's FreeStyle Libre, DexComm's G6 do not require calibration. **Proposed change:** "Currently these methods **<u>may</u>** still require traditional blood glucose measurements for calibration and it needs to be taken into consideration that glucose measurements from the interstitial fluid lag temporally behind blood glucose values."	Text deleted
Line 293	1	**Comment:** Refer to treatment satisfaction as that is the language of an instrument like TSQM. **Proposed change:** change 'assess treatment burden' to 'assess treatment burden **and satisfaction'**	Accepted.
Line 320	1	**Comment**:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		FPG is proposed as the primary evaluation criterion for dose-ranging study. Probably PPG should be mentioned for drugs with a short duration of action.	
Line 324	1	**Comment:** **4.4.4.1. General design elements** As standard of care is not the same in all countries this indicates that background treatment will not be the same for all subjects included if the guidance text is to be followed - which for confirmatory trial likely will not be appropriate. Hence background treatment needs in some way to be in alignment with the need for obtaining the indication(s). **Proposed change:** Suggest to change text in line 333 and 336 from "standard of care" to "established therapy" since standard of care can differ between countries/regions in multiregional clinical trials cf. ICH-E17.	Accepted
Line 341	1	**Comment:** **4.4.4.1. General design elements** Effect could also be on microvascular risk factors - e.g. albuminuria. **Proposed change:** Please add text to line 341 "and/or microvascular risk factors - e.g. albuminuria".	Not relevant anymore; text has been changed
Line 345	1	**Comment:** It is suggested to expand the margin of HbA1c referred to in section **4.4.4.1 General design element** in the current version of the guideline from the present 0.3% (3 mmol/mol) to a range of 0.3-0.4% (3-4 mmol/mol). The	Not Accepted. It is said that a margin of 0.3% is generally acceptable; this leaves room for argumentations for other margins.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		rationale for this proposal is to have a global harmonized approach to global development of medicinal products for diabetes; e.g. FDA and PMDA accept this range. The relevant margin will depend on the active comparator and will be justified and therefore it is recommended to include a range. **Proposed change (if any):** When predefining a non-inferiority margin, it should be considered that even apparently small reductions in HbA1c have been shown to be clinically relevant in terms of risk reduction of diabetic complications. While a margin of 0.3% **or 0.4%** (3 mmol/mol **or 4 mmol/mol)** is generally considered as acceptable, the choice of the margin should always be discussed in the clinical context.	
Lines 346-347	1	**Comment:** The sentence "Other factors to consider are the expected benefit over placebo for the active comparator and the details of the trial design" appears out of context of the previous statements on non-inferiority margin. EFPIA would welcome some clarification or editorial changes to make this sentence more interpretable.	Accepted.
Lines 347-350	1	**Comment:** In the reference to view a non-inferiority evaluation in the context of other long-term benefits, this should not be limited to cardiovascular benefit but should include long term benefits on the onset and progression of long-term complications resulting from hyperglycaemia. **Proposed change:** "If non-inferiority cannot convincingly be demonstrated, it is necessary to balance the degree of the observed or potential inferiority against some other	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		clinical advantage regarding e.g. safety, tolerability, compliance, ~~and/or~~ improvement in cardiovascular risk profile **and/or long term benefits on the onset and progression of long term complications resulting from hyperglycaemia**."	
Line 351	1	**Comment:** Suggest to soften the below statement for therapeutic exploratory studies. **Proposed change:** The study(ies) **often will be composed of three periods (if applicable)**: ~~should include~~: a run-in period, a titration period and a maintenance period.	This section refers to confirmatory studies.
Line 373	1	**Comment:** Regarding the text in the parenthesis "(e.g. up to two years after diagnosis)': Suggest to delete this example as it could be misleading – patients with T2DM are often diagnosed many years after they have had the disorder. **Proposed change:** Suggest to delete text in parenthesis.	Accepted
Line 375	1	**Comment:** Text in the parenthesis '(e.g. less than 8.5%': Suggest instead to recommend patients who are well-controlled on only one antidiabetic drug. Patients may be well-controlled because they are on multiple antidiabetic therapy, and it would therefore not be optimal (and not ethical) to set these patients on monotherapy.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Suggest to delete the text in the parenthesis: "(e.g. less than 8.5% [69 mmol/mol])"	
Line 381	1	**Comment:** Line 383-385 indicates that to get a first line treatment indication we need to: "In addition, beneficial effects on micro/ and/or macrovascular endpoints and a well characterized safety profile (including data on long term safety) should be documented before a first line monotherapy indication would be considered approvable." It is unclear why the requirement for the monotherapy indication is different from obtaining approval for an add-on or combination indication. As HbA1c is acknowledged as a valid biomarker, a head to head comparison against metformin demonstrating non-inferiority (or superiority) with respect to HbA1c should be regarded as sufficient. **Proposed change:** Suggest to delete the following sentence in line with comment above and those made in general comment: "~~In addition, beneficial effects on micro and/or macrovascular endpoints and a well characterized safety profile (including data on long term safety) should be documented before a firstline monotherapy indication would be considered approvable".~~	Accepted.
Line 398	1	**Comment:** For this part and in general - it could also be the maximal effective dose based on the investigator assessment(s). **Proposed change:**	Not accepted. Current text satisfactory enough.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Suggest to rephrase text in line 398 to read "… maximal tolerated, maximal effective or recommended dose".	
Line 415	1	**Comment:** "Less frequently, patients already receiving insulin may benefit from adding another glucose-lowering agent" in section 4.4.4.4. Combination with insulin: This statement is unfortunate. In light of the effect of other glucose-lowering agents e.g. GLP-1 agonists and SGLT2 inhibitors all T2DM patients with insulin treatment should be re-evaluated for switch to another glucose-lowering agent or in combination with insulin. All new clinical evidence point in this direction. **Proposed change:** Suggest to delete "Less frequently," in the sentence.	Accepted.
Line 425	1	**Comment:** "…. test agent should be added in patients with type 2 diabetes inadequately controlled on a reasonable dose of insulin…" in section **4.4.4.4. Combination with insulin.** **Proposed change:** Recommend to add the following text, after line 428: "If the effect of the test drug has been established in type 2 diabetes patients in other confirmatory trials, a general combination therapy with insulin claim should be allowed based on insulin added to patients inadequately controlled on a safe dose of the test agent."	The section has been shortened and updated
Line 430	1	**Comment:**	The section has been shortened and updated

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Do not understand why this is an insulin specific requirement - and in T2DM it should be known duration of diabetes. **Proposed change:** Suggest to revise text in line 428 to read: "Treatment groups should be balanced with respect to baseline anti-diabetic treatment" for clarity.	
Line 440	1	**Comment:** Wording 'body weight': Consider to add 'waist circumference'. **Proposed change:** Suggest rewording to read: "with focus on severe events, change in body weight and/or waist circumference."	Section was deleted.
Line 443 and 633	1	**Comment:** Gestational diabetes (GDM), Maturity Onset Diabetes of the Young (MODY), Latent Autoimmune Diabetes in Adults (LADA) and secondary diabetes are not described in the document. **Proposed change:** EFPIA recommends adding dedicated guidance on clinical investigation of medical products in gestational diabetes (GDM), Maturity Onset Diabetes of the Young (MODY) and Latent Autoimmune Diabetes in Adults (LADA). Could be as an additional subsection to the existing Sections 4.5 + 5.5 "Studies in special populations" or as new sections under section 7 "Other potential claims"	Not accepted as it is considered outside the scope of this revision.
Lines 468-470	1	**Comment:**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please clarify age ranges in this sentence: "Currently, the incidence and prevalence of type 2 diabetes is very low in children ≤ 10 years of age. As the mean age of type 2 DM development in children is 13 – 14 years, it is recommended that trials be performed in patients 10 to less than 18 years old." **Proposed change:** " …it is recommended that trials be performed in patients **≥**10 ~~to less than~~ **and <**18 years old."	
Lines 485-487, also lines 643-644.	1	**Comment:** It should be clarified that "significant safety concerns" should be based on data from the adult studies, and not simply theoretical concerns. In general, a delay in paediatric studies until after a product is on the market may undermine the ability to conduct an adequately controlled study due to the early "off label" use of the product by paediatric practitioners. Specify what kind of postmarketing experience is needed to decide on initiating paediatric trials. For example, adequate risk characterisation or measurement of the effectiveness of additional risk minimization measures (PASS results evaluated). **Proposed change:** Lines 485-487: If significant safety concerns **(based on data from adult studies)** exist for a given medicinal product it is not recommended that clinical trials including children are initiated before post marketing experience in adults is available.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 495-498	1	**Comment:** As currently written, it could be interpreted to mean that the special efforts should be limited to capturing influence on immune status, tumor-inducing effects and infections/inflammations (e.g. pancreatitis). **Proposed change:** "This could include **- but not limited to -** possible influence on immune status, tumour-inducing effects and 497 infections/inflammations (e.g. pancreatitis).	Not accepted. The sentence is already open to other alternatives.
Line 512	1	**Comment:** The age groups presented in line 512 (section **4.6.2. Hypoglycaemia**) are not aligned with the age groups in section 4.5.1 and in section 5.5.1. The geriatric age groups mentioned in Sections 4.5.1 and 5.5.1 are aligned with ICH E7. **Proposed change:** It is therefore recommended to align the age group cut-offs mentioned in section **4.6.2. Hypoglycaemia** line 512 with the cut-offs in Sections 4.5.1 and 5.5.1.	Accepted.
Line 531	1	**Comment:** "Anti-drug antibody incidences should be monitored over time." **Proposed change:** Suggest to change text in line 530-531 to read "…should be assessed including antibody incidence …." to be aligned with text in line 670.	Accepted.
Lines 564-565	1	**Comment:**	Methods to assess efficacy has been deleted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"(see also section 4.2 concerning definition of the scientific question of 564 interest)" Reference to section 4.3 could be added (for methods to assess efficacy).	
Line 569	1	**Comment:** Same comment as to in Line 224: Given the importance placed on glucose variability (particular time spent out of the ideal glucose range) it's recommended to add other glycaemic endpoint components such as variability in glycaemia (time in range by CGM/FGM, 1.5-anhydroglucitol). **Proposed change:** "In addition to the evaluation of the overall blood glucose control by HbA1c, at least 7-point capillary-blood glucose profiles (before and after each meal, at bedtime and **potentially** during the night) **and other glycaemic endpoint components such as variability in glycaemia (time in range by CGM/FGM, 1.5-anhydroglucitol)."**	Not accepted as it is considered outside the scope of this revision
Line 572	1	**Comment:** It is unclear why only paediatric population is referred for CGM. **Proposed change:** Alternatively, continuous glucose monitoring could be considered, ~~particularly~~ in **subgroups of patients with type 1 diabetes** (e.g. paediatric patients) **and in selected population with type 2 diabetes**.	Accepted-
Line 585	1	**Comment:** **5.4.1 Pharmacokinetics**	Cannot identify the basis for this comment

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This is not always possible e.g. for once weekly insulins - so what is to be done in such situations? **Proposed change:** Suggest to add "if possible" after "under development" in line 586.	
Line 639	1	**Comment:** **5.5.2 Children** "Since type 1 diabetes predominantly develops in children and adolescents": This is actually not a true statement. **Proposed change:** It would be more adequate to state 50% <age 30 and 50% >age 30. It would be better to acknowledge that the clinical context within which half of the patients with T1DM is particularly vulnerable and that this also impacts on clinical drug development.	Accepted.
Line 648	1	**Comment:** CGM time in range should be allowed as primary endpoint if justified (see also **Key comment**). **Proposed change:** Suggest to add this in this section **5.5.2 Children**	Not accepted. There is currently no consensus about this.
Line 651	1	**Comment:** Should 'ketoacidosis' be considered as an assessment parameter'? Consider to add new subsection on ketoacidosis as safety aspect in Sections 4.6. and 5.6.	Not accepted as it is considered outside the scope of this revision

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 654-655	1	**Comment:** A cross reference to section 4.6.2 and also to the definitions (lines 877-916) is required to emphasize the importance of using definitions of hypoglycaemia according to Learned Societies. **Proposed change:** "Incidence and rate of both overall and severe hypoglycaemia should be determined in all clinical trials **(see sections 4.6.2 and "Definitions"**.	Accepted.
Lines 662-665	1	**Comment:** This sentence and especially the phrase "provided that this is not achieved with simply allowing HbA1C to rise" is confusing. Also, not clear why this discussion is limited to insulin comparators. **Proposed change:** A relevant reduction of documented episodes of hypoglycaemia ~~(especially severe events)~~, particularly severe events, ~~if studied~~ in appropriately controlled **clinical** trials, could support a claim of superiority over the ~~insulin used a s~~ comparator provided that ~~this is not achieved with simply allowing HbA1c to rise~~ **the lower incidence of hypoglycaemia is not associated with increased HbA1c with the investigational agent**."	Accepted.
Lines 667-668	1	**Comment:** Consider stating that this is important for monoclonal antibodies and siRNA.	Not accepted. Outside scope of this section.
Line 705	1	**Comment:**	Accepted. Added to section 5.3.1.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Section **6, Non-insulin medicinal products…**: PROs are only mentioned in Section 4 for non-insulin type 2 products (i.e. section 4.5.2). However, assessment of PROs is also relevant for insulin products and non-insulin products for T1DM. **Proposed change:** Suggest to add PROs to both of these sections (i.e. Section 5 and 6, respectively.	
Line 711	1	**Comment:** If ATMP (advanced therapy medicinal products such as e.g. stem cell therapy) are in scope for this guideline. **Proposed change:** Then the following comment is applicable: "In order to confirm such benefits, phase III studies should be placebo controlled and an initial run-in period…" This approach with placebo-controlled studies might not be ethical when performing studies with some ATMPs (advanced therapy medicinal products such as e.g. stem cell therapy). Suggest to rephrase to "Generally, in order to confirm such benefits, phase III studies …. However, for new advance therapy medicinal products, placebo-controlled studies may not be ethical and if justified active controlled studies could be accepted."	Not accepted. It is not understood why placebo-control is not adequate for ATMP.
Lines 720-722	1	**Comment:** The proposed guideline provides the possibility to use composite safety-and-efficacy endpoint as secondary one. Such endpoints are relevant for the patient and prescriber, and incorporate benefit-risk balance in a single measurement.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Include the possibility to use composite safety-and-efficacy endpoints as primary ones. Consider the relevance of such endpoints also for insulin products (section 5.3.1), or even for type 2 diabetes mellitus (section 4.2.1) for products with severe identified risks. "Defining a composite endpoint encompassing HbA1c decrease and risk of hypoglycaemia (e.g. "HbA1c <7% without documented symptomatic hypoglycaemia" or "HbA1c <7% without nocturnal or severe hypoglycaemia") could be included as a secondary endpoint. **Additional secondary endpoints may be considered if scientifically justified (e.g. time in range).**"	
Lines 722-725	1	**Comment:** Although patients with T1DM are usually more lean, weight gain related to insulin treatment is of concern for patients, therefore weight neutrality/weight loss is relevant to be assessed as a separate endpoint and also as part of the composite endpoint. Another important endpoint which has gained more attention in the clinical practice is blood glucose time in range, based on continuous glucose monitoring (CGM). **Proposed change:** Include the possibility to assess weight neutrality/weight loss both as a separate secondary endpoint and as part of the composite endpoint. Include the possibility to assess glucose time in range as a secondary endpoint.	Partly accepted.
Line 756-759, and lines 797-798	1	**Comment:** In general, the field of paediatric research is moving away from a routine "step down approach" to where there must be a justification for such an approach given the inevitable delay in making the product available to younger children.	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		In other words, a "step down approach" should not be recommended unless there are specific safety reasons to adopt such an approach. **Proposed change:** ~~For safety reasons, a~~ **A** step down approach within the paediatric population is recommended **only where a specific safety concern warrants this.** ~~i.e.~~ **In the absence of** such a safety concern, commencing studies in younger age groups only if efficacy and particularly relevant safety data are available from older subjects (e.g. 12-<18 y., 6-<12 y.; 1-<6 y.)~~.~~ **is not required.**	
Lines 875-876	1	**Comment:** The word "impaired" is missing. **Proposed change:** "In the absence of symptoms, diabetes/impaired glucose tolerance or **impaired** fasting glucose should not be diagnosed on a single glucose measurement but needs confirmation."	Accepted.
Line 20	1	**Comment:** Section title inconsistent with section 6. **Proposed change:** 'of novel glucose lowering medicinal products'.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 66	1	**Comment:** Section title is inconsistent. **Proposed change:** Be consistent between use of 'medicinal products' and 'glucose lowering agents' also used previously.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 88	1	**Comment:** Type 1 diabetes is the result of autoimmune pancreatic beta cell destruction. **Proposed change:** Type 1 diabetes is the result of **autoimmune** pancreatic beta.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 108	1	**Comment:** As stated in Line 106 in children and adolescents, the diagnosis of type 1 and type 2 is similar to that in adults. **Proposed change:** "…between type 1 and type 2 diabetes in children **and adolescents**, see relevant guidelines…"	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 159	1	**Comment:** Clarify target population **Proposed change:** Change to '... representative of the intended target population'	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 162	1	**Comment:** Randomization aims to balance factors but cannot guarantee it. **Proposed change**: Change 'Randomisation should…' to 'Randomisation aims to balance…'	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 206	1	**misspelling: 'principle' should be 'principal'**	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 227	1	**Comment:** Please consider to spell out AUC first time mentioned.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Lines 230-232	1	**Comment:** This paragraph would need to be clarified by providing a few more specifics. Besides two minor revisions are proposed below for more clarity. **Proposed change:** "Depending on the mode of action of the test agent and risk for hypoglycaemia ~~of~~ **in** the study population, particularly **for** nocturnal hypoglycaemia,…"	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 319	1	**Comment:** Proposal to clarify "…at least 8 weeks and usually up to 3 months" **Proposed change:** "…at least 8 weeks and usually up to ~~3 months~~ **12 weeks**"	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 509	1	**Comment:** Text in section **4.6.2. Hypoglycaemia** should be corrected from: "…self-monitored blood glucose (see also sections 5.6.1 and 8.2)." **Proposed change** to: "…self-monitored blood glucose (see also sections 5.6.1 and Definitions)." Since there is no section 8.2 in the document.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 512	1	**Comment:** "for" is the wrong preposition. **Proposed change:** "…stratified ~~for~~ **by** age"	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 559-560	1	**Comment:** *"(see section 4.5)"* Do you mean section 5.5?	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 660	1	**Comment:** *"(see section 8.2)"* Section 8.2 does not exist.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 718	1	**Comment:** Spelling error in line 718 i.e. Hb1Ac	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Line 894	1	**Comment:** Suggest putting "it should be noted that…. Therefore the use of other additional…." together and in separate paragraph. **Proposed change:** It should be noted that glycaemic thresholds for responses to hypoglycaemia vary and thus symptoms of hypoglycaemia can occur at higher glycaemic levels, in particular in patients with poor glycaemic control. Therefore the use of other additional glycaemic thresholds and capturing of symptoms suggestive of hypoglycaemic symptoms can be considered.	Editorial comments have not been taken into account since the number of the lines have changed so much during the revision.
Lines 88-91	3	**Comment:** JDRF suggest including that T1D is an autoimmune disease and acknowledging non-insulin therapies. We also recommend expanding this section to include comments acknowledging the unmet need that still exist in type 1 diabetes. **Proposed change (if any):**	Not accepted as it is considered outside the scope of this revision.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Type 1 diabetes is the result of autoimmune pancreatic beta cell destruction and is prone to acute complications, such as ketoacidosis. In type 1 diabetes the main goal is optimal blood glucose control to be achieved by ~~optimal~~ the best possible insulin replacement therapy, addition of non-insulin glucose lowering therapies in some patients and extensive education and disease management. Significant unmet needs still exist in type 1 diabetes. Despite advances in insulin therapy and technologies to both administer insulin and monitor blood glucose, only 30% of people or less in the United States of America with T1D are achieving American Diabetes Association recommended outcomes. This data comes from the T1D Exchange which is a diabetes speciality clinical based registry, so it is a safe assumption that those not seen in speciality clinics do worse[2]. CGM has been shown to be a beneficial tool[3] but adoption has not been that great.[4] Similar data is not available for the EU. Hypoglycaemia and diabetic ketoacidosis (DKA) remain important barriers to achieving glycaemic control. Prevention of complications and management of pregnancy are also important issues.	
Line 188-192	3	**Comment:** JDRF suggests including additional information on HbA1c and the consensus of the type 1 diabetes community that additional outcome measures beyond HbA1c are important. Representatives from the EMA have participated and presented at meetings[5,6] where the diabetes community has clearly stated that benefits of therapies on outcomes beyond HbA1c, such as hypoglycaemia and	Partly accepted, but HbA1c is still considered as an adequate primary endpoint

[2] Diabetes Care. 2015 Jun;38(6):971-8. doi: 10.2337/dc15-0078
[3] N Engl J Med 2008; 359:1464-1476. DOI: 10.1056/NEJMoa0805017
[4] Clinical Diabetes 2017 Nov; cd170053. https://doi.org/10.2337/cd17-0053
[5] FDA Meeting. Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c). August 29, 2016. FDA White Oak Campus
[6] DiaTribe Foundation Meeting. *Glycemic Outcomes Beyond A1c: Standardization and Implementation*. July 21, 2017. Bethesda North Marriott Hotel and Conference Center

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		time in range, are important and we ask that the guideline be updated to reflect this. **Proposed change (if any):** Glycated haemoglobin (HbA1c) is the most widely accepted measure of overall, long-term blood glucose control in patients with diabetes. While ~~I~~it reflects the mean glucose concentration over the past 2-3 months, it does not capture short-term, yet impactful, variations in blood glucose excursions in individuals with type 1 diabetes. Reduction of HbA1c is known to reduce the long-term risk of development of microvascular complications. Therefore, HbA1c is an appropriate primary endpoint to support a claim based on glycaemic control. Additional outcome measures such as hypoglycaemia and time in range may also be considered to support claims of glycaemic control.	
Lines 230-232	3	**Comment:** JDRF strongly recommends that the guideline recognize that continuous glucose monitoring provides additional relevant information not only for nocturnal hypoglycaemia, but rather for all hypoglycaemia, regardless of the time of day, as well as for hyperglycaemia and time in range. **Proposed change (if any):** Depending on the mode of action of the test agent and risk for hypoglycaemia of the study population, ~~particularly nocturnal hypoglycaemia,~~ continuous blood glucose monitoring should be considered to provide additional relevant information.	Accepted.
Line 271-275	3	**Comment:**	Acknowledged, but not amended due to the structure of the Guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		This section does not seem to apply to type 2 diabetes and appears redundant to Section 4.3.2. JDRF suggests that Section 4.2.5 be deleted and the language from this section be combined/added to the language that appears in Section 4.3.2 which is most appropriate. The changes to reflect the combination JDRF proposes are provided below (see Comment for Lines 293-295). **Proposed change (if any):** ~~The use of disease-specific patient-reported outcomes for diabetes is recommended as it may reveal important information on how a treatment affects quality of life. Furthermore, such information will help to contextualize observed effects on measures derived from continuous glucose monitoring such as glucose variability, glucose excursions and time spent in normal range.~~	
Line 283-288	3	**Comment:** While this language appears in the type 2 diabetes section of the guideline, the type 1 diabetes section often refers to this section so the T1D Outcomes Program Steering Committee's comments are to make this broadly applicable to both type 1 and type 2 diabetes. We are aware of the approval in the EU of a continuous glucose monitoring system that does not require calibration. Additionally, continuous glucose monitoring (CGM) devices are designed to account for the lag between glucose in interstitial fluid and glucose in blood, so the lag is not clinically meaningful. CGMs are able to alert patients to hypoglycaemic and hyperglycaemic events. There are also systems available in which the data derived from the CGM is used to halt the administrations of insulin for impending hypoglycaemia and in some systems, CGM data is used to automatically calculate continuous doses of insulin. **Proposed change (if any):**	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		For recording of plasma glucose, capillary glucose is acceptable provided that there is confidence in the quality of the glucose measurements. However, the use of devices allowing continuous blood glucose monitoring is encouraged and regarded as useful in adults[7] and children[8] to describe ~~overnight~~ glucose profiles (both hypoglycaemia and hyperglycaemia). Currently, some of these methods still require traditional blood glucose measurements for calibration. It should be noted that although glucose measurements from the interstitial fluid lag temporally behind blood glucose values, this lag is accounted for in the continuous glucose monitoring technologies allowing them to alert patients to hypo- and hyperglycaemic events. Some insulin pump systems use continuous glucose monitoring data to suspend insulin delivery (predictive low glucose suspend) and to dose insulin continuously.	
Lines 293-295	3	**Comment:** Please refer to our comment for Lines 271-275. JDRF suggest consolidating the Patient-reported outcomes information into Section 4.3.2. **Proposed change (if any):** The inclusion of patient-reported outcomes to assess the treatment burden and impact on daily life, diabetes management, compliance and cognition is recommended. In this case it is important that the questionnaires or scales are validated for use in the setting of diabetes. Furthermore, such information will help to contextualize observed effects on measures derived from continuous glucose monitoring such as glucose variability, glucose excursions and time spent in range.	Partly accepted.

[7] http://care.diabetesjournals.org/content/diacare/early/2017/01/18/dc16-2482.full.pdf/
[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5467105/

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 411-442	3	**Comment:** JDRF recommends the Agency make it clear that this section is only relevant for T2D combination with insulin therapies (drug + insulin) and does not apply to T1D combinations with insulin therapies. The document largely provides guidance that is T2D-specific, such as failure of X or X+Y, following which insulin can be started, etc. It does not have relevance to T1D, such as with the use of adjunct treatments. **Proposed change (if any):** Other study designs are principally possible. In such cases EMA scientific advice is recommend. Refer to section 5.6.4 for T1D combinations with insulin therapies.	Section 4 only refer to T2D. This is reflected in the section title.
Lines 505-510	3	**Comment:** Learned Societies, such as the International Hypoglycaemia Study Group (IHSG), the European Association for the Study of Diabetes (EASD), the American Diabetes Association (ADA), and the Steering Committee of the T1D Outcomes Program, have recently come to consensus on a standardized definition for hypoglycaemia that does not include symptoms as part of the definition. JDRF recommends the guideline be updated here and in Sections 5.6.1 and the Definitions/Section 8.2 to reflect the consensus reached by the Learned Societies. Please note that Section 8.2 is referred to in several places throughout the guideline, but it does not exist in the document. In our comments, we have assumed Section 8.2 is the Definitions section. Henceforth we will refer to it as Definitions/Section 8.2. **Proposed change (if any):** In type 2 diabetes, episodes of severe hypoglycaemia associated with severe CNS dysfunction are rare, but may be of particular concern in	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		children/adolescents and in ~~the elderly~~ older adults. A standardised definition of severe and less severe episodes of hypoglycaemia should be used as defined by Learned Societies to include ~~a set of symptoms and~~ a given level of self-monitored blood glucose (see also sections 5.6.1 and Definitions/Section 8.2). Hypoglycaemia should be confirmed by measuring capillary or plasma glucose levels whenever possible. There should be confidence in the quality of the glucose measurements.	
Lines 566-579	3	**Comment:** JDRF recommends the Agency expand its thinking and use of continuous glucose monitoring (CGM) data, particularly as it relates to the capture of outcomes beyond HbA1c that the type 1 diabetes community and Learned Societies have defined as clinically meaningful, such as time in normal range (or "Time in Range") and hypoglycaemia. As noted in this section, rapid changes in plasma glucose occur in patients with type 1 diabetes. Fasting, postprandial and 7-point glucose measurements are not able to capture these rapid and often times, short term changes, accurately. The best tool with the ability to capture this information is continuous glucose monitors and we recommend the Agency place additional emphasis on their use in clinical trials for therapies seeking an indication of glycaemic control in patients with type 1 diabetes, regardless of age and regardless of time of day, to give a true representation of a continuous glucose profile. Please refer to the comment above for Lines 283-288 which details the utility of CGM data as well. The T1D Outcomes Program is a multi-disciplinary program including representatives of all T1D stakeholders including a Steering Committee made up of representatives from diabetes clinician organizations and research funders, including the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Association, the Endocrine Society, JDRF, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the T1D Exchange. The T1D Outcomes Program developed consensus definitions for a set of priority outcomes for T1D in addition to HbA1c which was published[9] in Diabetes Care in November 2017. In particular for "Time in Range", the T1D Outcomes Program Steering Committee determined that an individual with blood glucose levels that rarely extend beyond the thresholds defined for hypo- and hyperglycaemia is less likely to be subject to the short-term or long-term effects experienced by those with frequent excursions beyond one or both thresholds. It was also determined that time in range has the following characteristics: • Captures fluctuations in glucose levels continuously compared to HbA1c • Is more specific and sensitive than traditional HbA1c testing • Is more likely to be comparable across patients than HbA1c values • May be more likely than HbA1c levels to correlate with patient reported outcomes. Additionally, weight gain is common in type 1 diabetes patients due to intensive insulin therapy and JDRF recommends the evolution of body weight gain also be considered in type 1 diabetes studies. **Proposed change (if any):** However, the rapid changes in plasma glucose levels that occur, particularly in type 1 diabetes, call for some specific considerations: • Both fasting and postprandial blood glucose levels should be measured as secondary endpoints. Other glycaemic endpoint components such as time in range and glycaemic variability are also encouraged.	

[9] Diabetes Care 2017 Dec; 40(12): 1622-1630. https://doi.org/10.2337/dc17-1624

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• In addition to the evaluation of the overall blood glucose control by HbA1c, continuous glucose monitoring is encouraged. Alternatively, at least 7-point capillary-blood glucose profiles (before and after each meal, at bedtime and during the night) at regular intervals are necessary, particularly in type 1 diabetes~~ic~~ patients. ~~Alternatively, continuous glucose monitoring could be considered, particularly in paediatric patients.~~ • Reduction in the amplitude between postprandial hyperglycaemic peaks and fasting blood glucose values is desirable, but will not be accepted as a claim of superiority of a new insulin compared to an established insulin, unless accompanied by a relevant improvement in blood glucose control (measured by HbA1c), time in range, hypoglycaemia or other clinically meaningful outcomes (refer to Definitions/Section 8.2). Weight gain is frequent in diabetic patients trying to implement intensive glucose control. The evolution of body weight will also be taken into account in the global evaluation of the efficacy and safety~~, particularly in type 2 diabetic patients~~.	
Lines 599-602	3	**Comment:** Please refer to the comment and proposed change above for Lines 566 – 579 related to JDRF's recommendation that the Agency expand its thinking and use of continuous glucose monitoring data for the capture of clinically meaningful outcome measures such as time in range and hypoglycaemia. **Proposed change (if any):** Insulin analogues are usually developed for their novel pharmacokinetic and pharmacodynamic properties. Differences in parameters of PK/PD activity alone should however not be used to claim superiority over a comparator unless	No additional changes are considered needed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		associated with better HbA1c or other statistically significant and clinically relevant benefits e.g. regarding weight or time in range or hypoglycaemia.	
Lines 648-650	3	**Comment:** JDRF is pleased that the Agency prefers the use of continuous glucose measurements to capture glycaemic variability and hypoglycaemia data. Consistent with JDRF's recommendations for changes to Section 5.3 (see comments and proposed changes to Lines 566 – 579), we encourage the Agency to expand its thinking and utilization of continuous glucose monitoring data to capture time in range information as a clinically meaningful outcome measure. **Proposed change (if any):** HbA1c is the recommended primary efficacy endpoint. Time in range could also be considered, if justified.[10] Glycaemic variability, time in range and hypoglycaemic episodes are important secondary endpoints (see section 5.3). ~~Both~~ All should be documented, preferably by continuous glucose measurements.	Partly Accepted.
Lines 661-665	3	**Comment:** JDRF recommends the Agency expand its utilization of continuous glucose monitoring data to capture all hypoglycaemia, regardless of "severity" or time of day. All levels of hypoglycemia are clinically meaningful and affect the lives of patients with type 1 diabetes. The proposed change is meant to reflect the consensus reached by the Learned Societies (such as the IHSG, ADA, T1D Outcomes Program) on the definition and clinical significance of hypoglycaemia	No additional changes are considered needed.

[10] http://care.diabetesjournals.org/content/40/12/1622

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		beyond the previous definition of "severe" and states that blood glucose levels <3.0 mmol/L (<54 mg/dL) are clinically significant and therefore should be considered relevant. We also recommend that time in range be added as a clinically relevant outcome that can be captured via continuous glucose monitoring, similar to glycaemic variability, for the reasons stated for changes to Section 5.3 (see Lines 566-579). **Proposed change (if any):** In order to assess glucose variability, time in range and ~~nocturnal~~ hypoglycaemia, the use of continuous glucose monitoring devices should be considered. A relevant reduction of documented episodes of hypoglycaemia, ~~particularly severe events,~~ if studied in appropriately controlled trials, could support a claim of superiority over the insulin used as comparator provided that this is not achieved with simply allowing HbA1c to rise.	
Lines 683-694	3	**Comment:** JDRF recommends the Agency include some guidance on insulin dilution. We understand that insulin dilution is often used for treating paediatric patients and would like to get the Agency's perspective on this topic.	Not accepted as it is considered outside the scope of this revision.
Lines 707-728	3	**Comment:** Learned Societies such as (IHSG, ADA and the Steering Committee of the T1D Outcomes Program) have recently come to consensus on a standardized definition for hypoglycaemia that expands beyond the previous definition of "severe" and does not include symptoms as part of the definition. The proposed changes are meant to reflect this consensus on the definition and clinical significance of hypoglycaemia. We also recommend that time in range be added as a clinically relevant outcome for the reasons stated for changes to	Partly accepted. Time in range covered in previous sections.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Section 5.3 (see Lines 566-579). This section also mentions the risk of diabetic ketoacidosis (DKA) being closely followed during studies. JDRF recommends the Agency use the definition of DKA developed by the T1D Outcomes Program. This will facilitate consistency in research and clinical trials. JDRF also recommends the Agency add this standardized definition to Definitions/Section 8.2). **Proposed change (if any):** Insulin therapy is always required for the treatment of type 1 diabetes. However, the possibility of achieving glycaemic goals can be hampered by the risk of ~~severe~~ hypoglycaemia. New therapies that, in addition to insulin, may improve glycaemic control and/or reduce the risk of hypoglycaemia are being developed. In order to confirm such benefits, phase III studies should be placebo controlled and an initial run-in phase with the aim to optimize the insulin treatment is recommended. The preferred primary superiority endpoint should be the change from baseline HbA1c after approximately 26 weeks of double-blind treatment (see also section 4.2 concerning definition of the scientific question of interest). To show durability of the effect, a 6 month extension phase is required. Insulin doses should be adjustable during the study. It is also necessary to demonstrate that HbA1c decrease does not come at the cost of unacceptably increased hypoglycaemia risk. Alternatively, if non-inferiority testing of Hb1Ac vs. placebo on top of freely titrated insulin is the primary endpoint, incidence and/or rate of hypoglycaemia, or time in range should be a co-primary endpoint. Defining a composite endpoint encompassing HbA1c decrease, time in range and/or risk of hypoglycaemia (e.g. "HbA1c <7% without documented ~~symptomatic~~ hypoglycaemia" or "HbA1c <7% without nocturnal or severe hypoglycaemia")	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		could be included as a secondary endpoint. Reduction in insulin need alone is not regarded as a relevant endpoint. It has to be demonstrated that this is accompanied by clinically relevant changes such as reduced incidence of hypoglycaemia, increase in time in range or reduced body weight gain; however, the latter may be less relevant in patients with type 1 diabetes when they are lean and have a low degree of insulin resistance. Further, a reduction in insulin dose in insulin deficient patients could increase the risk of ketoacidosis. Therefore, the risk of diabetic ketoacidosis should be closely followed during the studies and measured using a standardized definition (refer to Definitions/Section 8.2).	
Line 739-747	3	**Comment:** It is unrealistic to have a pharmacological intervention or test agent with an absolutely benign safety profile. Every pharmacological intervention has some risks associated with it, however, those risks need to be carefully weighed against the potential benefits not only of the therapy but also against the risk of not intervening to prevent or delay the onset of a chronic condition in which there is still significant unmet need and where the burden of disease management for patients and their caregivers is life-long and severe. JDRF recommends the language be modified to reflect consistency with Lines 760-764. Biomarker qualification efforts are underway to provide predictive evidence for enrolling patients at high risk for developing type 1 diabetes. **Proposed change (if any):** Studies ~~suggest~~ show that approximately 15% of subjects with ~~only one~~a single autoantibody and approximately ~~5~~70% of subjects with ~~three or more~~multiple autoantibodies will develop type 1 diabetes in the course of	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		~~five~~ten years.[11] ~~Within the group of at-risk subjects with beta-cell specific autoantibodies, there are subgroups with even higher risk which can be identified based on insulin secretion and glucose tolerance.~~ Further stratification of risk within autoantibody positive individuals can be made utilizing measures of glucose tolerance or beta cell function.[12,13] Unless the test agent has a ~~an absolutely~~ rather benign safety profile, pharmacological intervention studies that aim to delay or prevent the onset of type 1 diabetes should only enrol patients who are at high risk of developing the disease. The validity for the choice of antibodies and other criteria should be properly justified prior to study start; notably the positive predictive values of such antibodies for development of type 1 diabetes should be sufficiently documented.	
Lines 756-759	3	**Comment:** JDRF suggest the Agency modify the current recommendation on conducting a step down approach in the paediatric population and consider the risk of developing diabetes in these clinical trials in addition to safety and efficacy data from older subjects. **Proposed change (if any):** For safety reasons, a step down approach within the paediatric population ~~is~~maybe recommended, i.e. commencing studies in younger age groups only if efficacy and particularly relevant safety data are available from older subjects (e.g. 12-<18 y., 6-<12 y.; 1-<6 y.) balanced by the low risk of developing diabetes. In the age group below one year, monogenic diabetes forms need to be executed.	Recommendation on step down has been revised

[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4878912/
[12] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321245/
[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4712442/

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 791-794	3	**Comment:** JDRF recommends that the Agency specify the use of continuous glucose monitors to capture a 24-hour glucose profile. **Proposed change (if any):** Any of these endpoints not included as co-primary endpoint should be evaluated as important secondary endpoint. Other secondary endpoints should include fasting and postprandial blood glucose concentrations, 24-hour glucose profiles (using continuous glucose monitoring is encouraged) and total daily insulin requirements. Occurrence of ketoacidosis should be recorded.	Accepted.
Lines 879-889	3	**Comment:** Learned Societies (such as IHSG, ADA and the Steering Committee of the T1D Outcomes Program) have recently come to consensus on a standardized definition for hypoglycaemia. JDRF recommends that the definitions for hypoglycaemia be updated to reflect the consensus of the Learned Societies. **Proposed change (if any):** Hypoglycaemia in adults The definitions of hypoglycaemia in individual protocols and across protocols within the development program should be standardized. One recommended approach for such standardization is to use the classification published by Learned Societies ~~the International Hypoglycaemia Study Group~~ (Diabetes Care 2017, 155-881 157 & Diabetes Care 2017 Dec; 40(12): 1622-1630): • Level 3 ~~Severe~~ hypoglycaemia: A~~n~~ severe event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient	Included definitions for adults and children refer to the International Hypoglycaemia Study Group and the ISPAD, respectively. Other approaches could also be accepted if well motivated

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. • Level 2~~Clinically important hypoglycaemia~~: A glucose level of less than 3.0 mmol/l (54 mg/dl) with or without typical symptoms of hypoglycaemia is considered sufficiently low to indicate serious, clinically important hypoglycaemia that needs immediate action. • Level 1 ~~Glucose alert value~~: A glucose alert value less than 3.9 mmol/l (70 mg/dl) that can alert a person to take action. This need not to be reported routinely in clinical studies, although this would depend on the purpose of the study. It should be noted that glycaemic thresholds for responses to hypoglycaemia vary and thus symptoms of hypoglycaemia can occur at higher glycaemic levels, in particular in patients with poor glycaemic control. Therefore the use of other additional glycaemic thresholds and capturing of symptoms suggestive of hypoglycaemic symptoms can be considered.	
Definitions/ Section 8.2 (New line numbers for TIR definition)	3	**Comment:** The T1D Outcomes Program prioritized Time in Range as one of the important outcomes beyond HbA1c and we recommend EMA include the T1D Outcome Program's consensus definition. As mentioned in one of our previous comments, the T1D Outcomes Program Steering Committee determined that an individual whose blood glucose levels that rarely extend beyond the thresholds defined for hypo- and hyperglycaemia is less likely to be subject to the short-term or long-term effects experienced by those with frequent excursions beyond one or both thresholds. It was also determined that time in range has the following characteristics:	Not accepted. Time in range measured by CGM has been included as an important endpoint, but since there is still not so much experience with this endpoint, a definition has not been included

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Captures fluctuations in glucose levels continuously compared to HbA1c • Is more specific and sensitive than traditional HbA1c testing • Is more likely to be comparable across patients than HbA1c values • May be more likely than HbA1c levels to correlate with patient reported outcomes. **Proposed change (if any):** Time in Range • Percentage of readings in the range of 70 mg/dL – 180 mg/dL (3.9-10.0 mmol/L) per unit of time	
Definitions/ Section 8.2 (New lines for DKA definition)	3	**Comment:** Diabetic Ketoacidosis (DKA) is mentioned throughout the guideline (lines 89, 727, 728, 794) as an important complication for people with diabetes, including monitoring its risk in clinical studies. The T1D Outcomes Program prioritized DKA as one of the important outcomes beyond HbA1c and we recommend EMA include the T1D Outcome Program's consensus definition. **Proposed change (if any):** Diabetic Ketoacidosis • Elevated serum or urine ketones (greater than the upper limit of the normal range), AND • Serum bicarbonate < 15 mmol/L or Blood pH < 7.3	Not accepted. We do not want to bind ourselves to one specific definition
Lines 88-91	4	**Comment:** The T1D Outcomes Program Steering Committee agrees with EMA's definition of type 1 diabetes, the goal for glucose control, and the importance of preventing complications. However, we recommend expanding this section to	We have decided to keep the introduction rather short. This is not a text book chapter.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		include comments acknowledging the unmet needs that still exist in type 1 diabetes. **Proposed change (if any):** Type 1 diabetes is the result of autoimmune pancreatic beta cell destruction and is prone to acute complications, such as ketoacidosis. In type 1 diabetes the main goal is optimal blood glucose control to be achieved by ~~optimal~~ the best possible insulin replacement therapy, addition of non-insulin glucose lowering therapies in some patients and extensive education and disease management. Significant unmet needs still exist in type 1 diabetes. Despite advances in insulin therapy and technologies to both administer insulin and monitor blood glucose, only 30% of people or less in the United States of America with T1D are achieving American Diabetes Association recommended outcomes. This data comes from the T1D Exchange which is a diabetes speciality clinical based registry, so it is a safe assumption that those not seen in speciality clinics do worse[14]. CGM has been shown to be a beneficial tool[15] but adoption has not been that great.[16] Similar data is not available for the EU. Hypoglycaemia and diabetic ketoacidosis (DKA) remain important barriers to achieving glycaemic control. Prevention of complications and management of pregnancy are also important issues.	
Line 188-192	4	**Comment:** The T1D Outcomes Program Steering Committee suggests including additional information on HbA1c and the consensus of the type 1 diabetes community that additional outcome measures beyond HbA1c are important.	The importance of other endpoints are reflected in the guideline

[14] Diabetes Care. 2015 Jun;38(6):971-8. doi: 10.2337/dc15-0078
[15] N Engl J Med 2008; 359:1464-1476. DOI: 10.1056/NEJMoa0805017
[16] Clinical Diabetes 2017 Nov; cd170053. https://doi.org/10.2337/cd17-0053

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Representatives from the EMA have participated and presented at meetings[17,18] where the diabetes community has clearly stated that benefits of therapies on outcomes beyond HbA1c, such as hypoglycaemia and time in range, are important and we ask that the guideline be updated to reflect this. **Proposed change (if any):** Glycated haemoglobin (HbA1c) is the most widely accepted measure of overall, long-term blood glucose control in patients with diabetes. While ~~I~~it reflects the mean glucose concentration over the past 2-3 months, it does not capture short-term, yet impactful, variations in blood glucose excursions in individuals with type 1 diabetes. Reduction of HbA1c is known to reduce the long-term risk of development of microvascular complications. Therefore, HbA1c is an appropriate primary endpoint to support a claim based on glycaemic control. Additional outcome measures such as hypoglycaemia and time in range may also be considered to support claims of glycaemic control.	
Lines 230-232	4	**Comment:** The T1D Outcomes Program Steering Committee strongly recommends that the guideline recognize that continuous glucose monitoring provides additional relevant information not only for nocturnal hypoglycaemia, but rather for all hypoglycaemia, regardless of the time of day, as well as for hyperglycaemia and time in range. **Proposed change (if any):** Depending on the mode of action of the test agent and risk for hypoglycaemia of the study population, ~~particularly nocturnal hypoglycaemia,~~ continuous blood	Accepted.

[17] FDA Meeting. Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c). August 29, 2016. FDA White Oak Campus
[18] DiaTribe Foundation Meeting. *Glycemic Outcomes Beyond A1c: Standardization and Implementation*. July 21, 2017. Bethesda North Marriott Hotel and Conference Center

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		glucose monitoring should be considered to provide additional relevant information.	
Line 271-275	4	**Comment:** This section does not seem to apply to type 2 diabetes and appears redundant to Section 4.3.2. The T1D Outcomes Program Steering Committee suggests that Section 4.2.5 be deleted and the language from this section be combined/added to the language that appears in Section 4.3.2 which is most appropriate. The changes to reflect the combination the T1D Outcomes Program Steering Committee proposes are provided below (see Comment for Lines 293-295). **Proposed change (if any):** ~~The use of disease-specific patient-reported outcomes for diabetes is recommended as it may reveal important information on how a treatment affects quality of life. Furthermore, such information will help to contextualize observed effects on measures derived from continuous glucose monitoring such as glucose variability, glucose excursions and time spent in normal range.~~	Acknowledged, but not amended due to the structure of the Guideline.
Line 283-288	4	**Comment:** While this language appears in the type 2 diabetes section of the guideline, the type 1 diabetes section often refers to this section so the T1D Outcomes Program Steering Committee's comments are to make this broadly applicable to both type 1 and type 2 diabetes. We are aware of the approval in the EU of a continuous glucose monitoring system that does not require calibration. Additionally, continuous glucose monitoring (CGM) devices are designed to account for the lag between glucose in interstitial fluid and glucose in blood, so	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the lag is not clinically meaningful. CGMs are able to alert patients to hypoglycaemic and hyperglycaemic events. There are also systems available in which the data derived from the CGM is used to halt the administrations of insulin for impending hypoglycaemia and in some systems, CGM data is used to automatically calculate continuous doses of insulin. **Proposed change (if any):** For recording of plasma glucose, capillary glucose is acceptable provided that there is confidence in the quality of the glucose measurements. However, the use of devices allowing continuous blood glucose monitoring is encouraged and regarded as useful in adults[19] and children[20] to describe ~~overnight~~ glucose profiles (both hypoglycaemia and hyperglycaemia). Currently, some of these methods still require traditional blood glucose measurements for calibration. It should be noted that although glucose measurements from the interstitial fluid lag temporally behind blood glucose values, this lag is accounted for in the continuous glucose monitoring technologies allowing them to alert patients to hypo- and hyperglycaemic events. Some insulin pump systems use continuous glucose monitoring data to suspend insulin delivery (predictive low glucose suspend) and to dose insulin continuously.	
Lines 293-295	4	**Comment:** Please refer to our comment for Lines 271-275. The T1D Outcomes Program Steering Committee suggest consolidating the Patient-reported outcomes information into Section 4.3.2. **Proposed change (if any):**	Partly accepted.

[19] http://care.diabetesjournals.org/content/diacare/early/2017/01/18/dc16-2482.full.pdf/
[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5467105/

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		The inclusion of patient-reported outcomes to assess the treatment burden and impact on daily life, diabetes management, compliance and cognition is recommended. In this case it is important that the questionnaires or scales are validated for use in the setting of diabetes. Furthermore, such information will help to contextualize observed effects on measures derived from continuous glucose monitoring such as glucose variability, glucose excursions and time spent in range.	
Lines 505-510	4	**Comment:** Learned Societies, such as the International Hypoglycaemia Study Group (IHSG), the European Association for the Study of Diabetes (EASD), the American Diabetes Association (ADA), and the Steering Committee of the T1D Outcomes Program, have recently come to consensus on a standardized definition for hypoglycaemia that does not include symptoms as part of the definition. The T1D Outcomes Program Steering Committee recommends the guideline be updated here and in Sections 5.6.1 and the Definitions/Section 8.2 to reflect the consensus reached by the Learned Societies. Please note that Section 8.2 is referred to in several places throughout the guideline, but it does not exist in the document. In our comments, we have assumed Section 8.2 is the Definitions section. Henceforth we will refer to it as Definitions/Section 8.2. **Proposed change (if any):** In type 2 diabetes, episodes of severe hypoglycaemia associated with severe CNS dysfunction are rare, but may be of particular concern in children/adolescents and in ~~the elderly~~ older adults. A standardised definition of severe and less severe episodes of hypoglycaemia should be used as defined by Learned Societies to include ~~a set of symptoms and~~ a given level of self-	Partly accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		monitored blood glucose (see also sections 5.6.1 and Definitions/Section 8.2). Hypoglycaemia should be confirmed by measuring capillary or plasma glucose levels whenever possible. There should be confidence in the quality of the glucose measurements.	
Lines 566-579	4	**Comment:** The T1D Outcomes Program Steering Committee recommends the Agency expand its thinking and use of continuous glucose monitoring (CGM) data, particularly as it relates to the capture of outcomes beyond HbA1c that the type 1 diabetes community and Learned Societies have defined as clinically meaningful, such as time in normal range (or "Time in Range") and hypoglycaemia. As noted in this section, rapid changes in plasma glucose occur in patients with type 1 diabetes. Fasting, postprandial and 7-point glucose measurements are not able to capture these rapid and often times, short term changes, accurately. The best tool with the ability to capture this information is continuous glucose monitors and we recommend the Agency place additional emphasis on their use in clinical trials for therapies seeking an indication of glycaemic control in patients with type 1 diabetes, regardless of age and regardless of time of day, to give a true representation of a continuous glucose profile. Please refer to the comment above for Lines 283-288 which details the utility of CGM data as well. In particular for "Time in Range", the T1D Outcomes Program Steering Committee determined that an individual with blood glucose levels that rarely extend beyond the thresholds defined for hypo- and hyperglycaemia is less likely to be subject to the short-term or long-term effects experienced by those with frequent excursions beyond one or both thresholds. It was also determined that time in range has the following characteristics: • Captures fluctuations in glucose levels continuously compared to HbA1c	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Is more specific and sensitive than traditional HbA1c testing • Is more likely to be comparable across patients than HbA1c values • May be more likely than HbA1c levels to correlate with patient reported outcomes. **Proposed change (if any):** However, the rapid changes in plasma glucose levels that occur, particularly in type 1 diabetes, call for some specific considerations: • Both fasting and postprandial blood glucose levels should be measured as secondary endpoints. Other glycaemic endpoint components such as time in range and glycaemic variability are also encouraged. • In addition to the evaluation of the overall blood glucose control by HbA1c, continuous glucose monitoring is encouraged. Alternatively, at least 7-point capillary-blood glucose profiles (before and after each meal, at bedtime and during the night) at regular intervals are necessary, particularly in type 1 diabetesic patients. ~~Alternatively, continuous glucose monitoring could be considered, particularly in paediatric patients.~~ • Reduction in the amplitude between postprandial hyperglycaemic peaks and fasting blood glucose values is desirable, but will not be accepted as a claim of superiority of a new insulin compared to an established insulin, unless accompanied by a relevant improvement in blood glucose control (measured by HbA1c), time in range, hypoglycaemia or other clinically meaningful outcomes (refer to Definitions/Section 8.2).	
Lines 599-602	4	**Comment:** Please refer to the comment and proposed change above for Lines 566 – 579 related to the T1D Outcomes Program Steering Committee's recommendation that the Agency expand its thinking and use of continuous glucose monitoring	No additional changes are considered needed.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		data for the capture of clinically meaningful outcome measures such as time in range and hypoglycaemia. **Proposed change (if any):** Insulin analogues are usually developed for their novel pharmacokinetic and pharmacodynamic properties. Differences in parameters of PK/PD activity alone should however not be used to claim superiority over a comparator unless associated with better HbA1c or other statistically significant and clinically relevant benefits e.g. regarding weight or time in range or hypoglycaemia.	
Lines 648-650	4	**Comment:** The T1D Outcomes Program Steering Committee is pleased that the Agency prefers the use of continuous glucose measurements to capture glycaemic variability and hypoglycaemia data. Consistent with the T1D Outcomes Program Steering Committee's recommendations for changes to Section 5.3 (see comments and proposed changes to Lines 566-579), we encourage the Agency to expand its thinking and utilization of continuous glucose monitoring data to capture time in range information as a clinically meaningful outcome measure. **Proposed change (if any):** HbA1c is the recommended primary efficacy endpoint. Time in range could also be considered, if justified.[21] Glycaemic variability, time in range and hypoglycaemic episodes are important secondary endpoints (see section 5.3). ~~Both~~ All should be documented, preferably by continuous glucose measurements.	Partly accepted.

[21] http://care.diabetesjournals.org/content/40/12/1622

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 661-665	4	**Comment:** The T1D Outcomes Program Steering Committee recommends the Agency expand its utilization of continuous glucose monitoring data to capture all hypoglycaemia, regardless of "severity" or time of day. All levels of hypoglycaemia are clinically meaningful and affect the lives of patients with type 1 diabetes. The proposed change is meant to reflect the consensus reached by the Learned Societies (such as the IHSG, ADA, T1D Outcomes Program) on the definition and clinical significance of hypoglycaemia beyond the previous definition of "severe" and states that blood glucose levels <3.0 mmol/L (<54 mg/dL) are clinically significant and therefore should be considered relevant. We also recommend that time in range be added as a clinically relevant outcome that can be captured via continuous glucose monitoring, similar to glycaemic variability, for the reasons stated for changes to Section 5.3 (see Lines 566-579). **Proposed change (if any):** In order to assess glucose variability, time in range and ~~nocturnal~~ hypoglycaemia, the use of continuous glucose monitoring devices should be considered. A relevant reduction of documented episodes of hypoglycaemia, ~~particularly severe events,~~ if studied in appropriately controlled trials, could support a claim of superiority over the insulin used as comparator provided that this is not achieved with simply allowing HbA1c to rise.	No additional changes are considered needed.
Lines 707-728	4	**Comment:** Learned Societies such as (IHSG, ADA and the Steering Committee of the T1D Outcomes Program) have recently come to consensus on a standardized	Partly accepted. Time in range is covered in previous sections.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		definition for hypoglycaemia that expands beyond the previous definition of "severe" and does not include symptoms as part of the definition. The proposed changes are meant to reflect this consensus on the definition and clinical significance of hypoglycaemia. We also recommend that time in range be added as a clinically relevant outcome for the reasons stated for changes to Section 5.3 (see Lines 566-579). This section also mentions the risk of diabetic ketoacidosis (DKA) being closely followed during studies. The T1D Outcomes Program Steering Committee recommends the Agency use the definition of DKA developed by the T1D Outcomes Program. This will facilitate consistency in research and clinical trials. The T1D Outcomes Program Steering Committee also recommends the Agency add this standardized definition to Definitions/Section 8.2). **Proposed change (if any):** Insulin therapy is always required for the treatment of type 1 diabetes. However, the possibility of achieving glycaemic goals can be hampered by the risk of ~~severe~~ hypoglycaemia. New therapies that, in addition to insulin, may improve glycaemic control and/or reduce the risk of hypoglycaemia are being developed. In order to confirm such benefits, phase III studies should be placebo controlled and an initial run-in phase with the aim to optimize the insulin treatment is recommended. The preferred primary superiority endpoint should be the change from baseline HbA1c after approximately 26 weeks of double-blind treatment (see also section 4.2 concerning definition of the scientific question of interest). To show durability of the effect, a 6 month extension phase is required. Insulin doses should be adjustable during the study. It is	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		also necessary to demonstrate that HbA1c decrease does not come at the cost of unacceptably increased hypoglycaemia risk. Alternatively, if non-inferiority testing of Hb1Ac vs. placebo on top of freely titrated insulin is the primary endpoint, incidence and/or rate of hypoglycaemia, or time in range should be a co-primary endpoint. Defining a composite endpoint encompassing HbA1c decrease, time in range and/or risk of hypoglycaemia (e.g. "HbA1c <7% without documented ~~symptomatic~~ hypoglycaemia" or "HbA1c <7% without nocturnal or severe hypoglycaemia") could be included as a secondary endpoint. Reduction in insulin need alone is not regarded as a relevant endpoint. It has to be demonstrated that this is accompanied by clinically relevant changes such as reduced incidence of hypoglycaemia, increase in time in range or reduced body weight gain; however, the latter may be less relevant in patients with type 1 diabetes when they are lean and have a low degree of insulin resistance. Further, a reduction in insulin dose in insulin deficient patients could increase the risk of ketoacidosis. Therefore, the risk of diabetic ketoacidosis should be closely followed during the studies and measured using a standardized definition (refer to Definitions/Section 8.2).	
Lines 791-794	4	**Comment:** The T1D Outcomes Program Steering Committee recommends that the Agency specify the use of continuous glucose monitors to capture a 24-hour glucose profile. **Proposed change (if any):** Any of these endpoints not included as co-primary endpoint should be evaluated as important secondary endpoint. Other secondary endpoints should include fasting and postprandial blood glucose concentrations, 24-hour glucose	CGM is encouraged in the guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		profiles (using continuous glucose monitoring is encouraged) and total daily insulin requirements. Occurrence of ketoacidosis should be recorded.	
Lines 879-889	4	**Comment:** Learned Societies (such as IHSG, ADA and the Steering Committee of the T1D Outcomes Program) have recently come to consensus on a standardized definition for hypoglycaemia. The T1D Outcomes Program Steering Committee recommends that the definitions for hypoglycaemia be updated to reflect the consensus of the Learned Societies. **Proposed change (if any):** Hypoglycaemia in adults The definitions of hypoglycaemia in individual protocols and across protocols within the development program should be standardized. One recommended approach for such standardization is to use the classification published by Learned Societies ~~the International Hypoglycaemia Study Group~~ (Diabetes Care 2017, 155-881 157 & Diabetes Care 2017 Dec; 40(12): 1622-1630): • Level 3 ~~Severe~~ hypoglycaemia: A~~n~~ severe event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. • Level 2~~Clinically important hypoglycaemia~~: A glucose level of less than 3.0 mmol/l (54 mg/dl) with or without typical symptoms of hypoglycaemia is	The definitions have been updated, see section 8 of the guideline

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		considered sufficiently low to indicate serious, clinically important hypoglycaemia that needs immediate action. • Level 1 ~~Glucose alert value~~: A glucose alert value less than 3.9 mmol/l (70 mg/dl) that can alert a person to take action. This need not to be reported routinely in clinical studies, although this would depend on the purpose of the study. It should be noted that glycaemic thresholds for responses to hypoglycaemia vary and thus symptoms of hypoglycaemia can occur at higher glycaemic levels, in particular in patients with poor glycaemic control. Therefore the use of other additional glycaemic thresholds and capturing of symptoms suggestive of hypoglycaemic symptoms can be considered.	
Definitions/ Section 8.2 (New line numbers for TIR definition)	4	**Comment:** The T1D Outcomes Program prioritized Time in Range as one of the important outcomes beyond HbA1c and we recommend EMA include the T1D Outcome Program's consensus definition. As mentioned in one of our previous comments, the T1D Outcomes Program Steering Committee determined that an individual whose blood glucose levels that rarely extend beyond the thresholds defined for hypo- and hyperglycaemia is less likely to be subject to the short-term or long-term effects experienced by those with frequent excursions beyond one or both thresholds. It was also determined that time in range has the following characteristics: • Captures fluctuations in glucose levels continuously compared to HbA1c • Is more specific and sensitive than traditional HbA1c testing • Is more likely to be comparable across patients than HbA1c values • May be more likely than HbA1c levels to correlate with patient reported outcomes. **Proposed change (if any):**	This comment is a repetition of a previous comment

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Time in Range • Percentage of readings in the range of 70 mg/dL – 180 mg/dL (3.9-10.0 mmol/L) per unit of time	
Definitions/ Section 8.2 (New lines for DKA definition)	4	**Comment:** Diabetic Ketoacidosis (DKA) is mentioned throughout the guideline (lines 89, 727, 728, 794) as an important complication for people with diabetes, including monitoring its risk in clinical studies. The T1D Outcomes Program prioritized DKA as one of the important outcomes beyond HbA1c and we recommend EMA include the T1D Outcome Program's consensus definition. **Proposed change (if any):** Diabetic Ketoacidosis • Elevated serum or urine ketones (greater than the upper limit of the normal range), AND • Serum bicarbonate < 15 mmol/L or Blood pH < 7.3	This comment is a repetition of a previous comment
613	6	**Comment:** It is unclear how (AUC, Cmax and Cmin) relates to the 24-h blood glucose profile. **Proposed change (if any):** Clarification is needed. If the 24-h blood glucose profile is assessed by Continuous Glucose Monitoring (CGM), then it would be good to make a statement like "Reporting according to a reported consensus is preferred (reference: Maahs, Diabetes Care 2016 pp 1175-9 or even better Agiostradtidou et al. Diabetes Care 2017;40:1622–1630). These consensus	It has been decided not to include this level of details

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		statements focus on type 1 diabetes, but CGM equally applies to type 2 diabetes. If the 24-h blood glucose profile is derived from self-measurements, it would be good to clarify whether postprandial excursions or absolute values are preferred. For this and all other comments, we would be happy to draft text or to answer/discuss any questions you may have.	
660	6	**Comment:** Reference is made to section 8.2, but no such section can be found in the document. **Proposed change (if any):** Is the 'Definitions' section line 877 and further meant?	It is now referenced as section 8.
234	6	**Comment:** The draft guideline supports the use of serum fructosamine as secondary endpoint in short-term clinical studies, however, it does not specify whether or not other markers of short-term glycaemic control are acceptable. **Proposed change (if any):** Serum fructosamine and other markers of acute glycaemic control such as 1,5-anhydroglucitol or glycated albumin can also be used as endpoints in short term studies.	Not accepted. The experience with other markers of short-term glycaemic control is limited
320	6	**Comment:** The focus on FPG in studies with a duration of 8-12 weeks is difficult to understand. This study duration should be long enough to see most of the effect on HbA1c. In addition, drugs acting primarily on postprandial glucose might have difficulties to show effects on FPG.	New text in GL; Glucose based metrics should be the primary evaluation criterion in dose-ranging studies of 8-12 weeks duration.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Consider to also allow for other primary endpoints, e.g. postprandial glucose excursions, HbA1c, fructosamine, 1,5-anhydroglucitol. Endpoints derived from 24-h blood glucose profiles as specified in section 5.4.3 are also good options, but see previous comment on this section.	
859	6	**Comment:** According to ADA Criteria for the diagnosis of diabetes: FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h. **Proposed change (if any):** Please consider to add time period of fasting to this criterion.	Accepted.
868-742	6	**Comment:** According to ADA Categories of increased risk for diabetes (prediabetes) FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG) 2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT) HbA_{1C} 5.7–6.4% (39–47 mmol/mol)	The definitions of IGT and IFG in the guideline are still valid
905 and 908	6	**Comment:** According to ISPAD CPC Guidelines for Hypoglycaemia plasma glucose concentration are used. **Proposed change (if any):** Please consider to revise BG to PG: BG level of ≤ 3.9 mmol/l (70 mg/dl)	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome

3. General comments on text of the Reflection paper released for consultation in 2022

Stakeholder number	General comment (if any)	Outcome (if applicable)
9	The main aim when treating patients with type 2 diabetes is to prevent or delay the micro- and macrovascular complications of diabetes, including long-term complications (*1*). Numerous glucose-lowering drugs have been authorised for use in type 2 diabetes in the European Union. Some of them, such as *metformin*, appear to have efficacy to reduce the clinical complications of diabetes and shall be considered as the standard of care until other drugs are shown to represent a tangible therapeutic advance (*1*, *2*). Whatever the clinical situation, any new drug authorised in the European Union should have been shown to represent a therapeutic advance. If not, it has nothing to offer in terms of improving the quality of patient care. To be qualified as a therapeutic advance, the drug may offer greater efficacy, based on clinical outcomes (mortality, morbidity, quality of life) or a better adverse effect profile, or may be tangibly easier or safer to use for the patient or whoever prepares or administers the drug. In situations in which standard-of-care treatments already exist, such as in type 2 diabetes, a new drug can only be shown to represent a clinical advance in comparison with one of these treatments. It is	It is not a regulatory requirement that a new drug must provide a benefit compared to what is already provided. The approval is based on the absolute, not relative, benefit/risk-balance.

Stakeholder number	General comment (if any)	Outcome (if applicable)
	therefore overwhelmingly in patients' interests that new drugs always be compared in trials with the standard-of-care treatment(s), pharmacological or non-pharmacological, based on clinical outcomes. It is not enough to show that the drug has a favourable effect on a surrogate outcome (such as a laboratory parameter) or has a similar harm-benefit balance to a drug already on the market, without offering any advantage in terms of efficacy, adverse effects, or ease and safety of use. Similarly, cases in which a new drug is only compared with placebo must be a soundly justified exception, in line with Article 33 of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects (*3*). Article 10 of this declaration stipulates that "*No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration*" (*3*). It is also important that new drugs are evaluated in at least two double-blind randomised clinical trials, in order to mitigate the consequences of sampling in each trial. Finally, "non-inferiority" trials are not designed to show whether the study drug is more effective than the comparator. Any evaluation of a new drug in this type of trial must therefore be a soundly justified exception.	

Stakeholder number	General comment (if any)	Outcome (if applicable)
10	The question regarding metformin comparison studies for obtaining a first-line treatment indication is relevant: Metformin has lost its role as unequivocal first-line medication for type 2 diabetes. We would favor the requirement for proof of effectiveness against diabetes complications in order to get this indication.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
10	1 and 2 In our opinion, comparison with metformin (or another active comparator, but not placebo) is still relevant 3 and 4 We do not feel that an effect on complications needs to be demonstrated for reasons already stated but if and only if safety has been or will foreseeably and quantitatively be documented (cf the FDA) We feel that, literally, placebo-controlled CVOTs in general cannot be done any more but we suppose what is meant is new product vs placebo on top of usual care. That is still feasible and ethical.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
10	1. Monotherapy - Although Met has lost some of its strength as universal first-line therapy, we would support metformin as an active comparator rather than placebo. As reasoned in the document, placebo may reduce the possibility to explore efficacy (and safety) in people with more severe hyperglycaemia at diagnosis. Moreover, may still be largely used in many countries. Also, we would be cautious to support proof of benefit on complications at this is practically unfeasible when a	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC. The guideline will not discuss first line combination treatment. This is instead reflected in the FDC guideline

Stakeholder number	General comment (if any)	Outcome (if applicable)
	monotherapy strategy may be envisaged: large population, very long follow-up. 2. Add-on therapy: option 1 sounds more practical but option 2 is more in line with current support for early combination therapy. If option 2 is going to be considered, the downside may be represented by the need of longer RCT with reduced rate of treatment failure (i.e. overcoming pre-defined A1c targets) as primary endpoint. 3. Fully agree.	

4. Specific comments on text of the Reflection paper released for consultation in 2022

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
54-55	1	**Comments:** 4th bullet "….demonstrate maintenance of effect over at least 12 months": A more precise definition is expected for the requirement. Time period to be clarified; we understand that the 12 months aim at the overall assessment period from baseline to end of months 12 as specified in the paragraph thereafter. **Proposed changes:** Please specify the meaning of "maintenance": It is our understanding that some effect of the new active drug observed at week 52 would fulfil this requirement. And is "maintenance" referred to here to the absolute delta vs the comparator or to the lowest level achieved without any rebound?	Not understood. "At least 12 months" seems clear enough. "Maintenance" is not defined or included in the SmPC.
104	1	**Comments:** "1) Is it still relevant to reflect the first line status of metformin in the therapeutic indication?" Given that worldwide diabetes guidelines e.g. ADA/EASD give recommendation to start after Diet and exercise with Metformin, if tolerated, the need of the monotherapy study should only be a recommendation instead of a mandatory requirement, unless a 1st line monotherapy study would be intended by the applicant. In our view it is no longer relevant to reflect the 1st line treatment of metformin, given that ADA/EASD standards recommend individualized treatment approaches, taking into account the individual risk of profile a patient and the cost effectiveness of a recommended treatment. Moreover, in specific patients *a priori* initiation of a combinational drug is even recommended. Therefore, the prominent position of metformin is no longer in line with scientific knowledge and clinical practice.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Furthermore, some treatment guidelines (for example, the 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD) recommend that other agents (GLP-1 RA or SGL2i) should be used in treatment naïve people with Type 2 diabetes with established CV disease or heart failure. In addition, it is unclear why the requirement for the monotherapy indication is different from obtaining approval for an add-on/combination indication. As HbA_{1c} is acknowledged as a valid biomarker, a head-to-head comparison against metformin demonstrating non-inferiority (or superiority) with respect to HbA_{1c} should be regarded as sufficient. **Proposed changes:** Thus, in the wording of the therapeutic indication it is no longer relevant to have only metformin as first line, and as such the language should be generalised. We also suggest to generally remove the requirement of intolerance or contraindications to metformin before other anti-diabetic treatments can be used as first line treatment.	
105-107	1	**Comments:** "2) With respect to glucose lowering effect; is it still of value/necessary to require a direct comparison to metformin or would a comparison to another approved treatment or even a comparison to placebo be enough to ensure a satisfactory glucose lowering effect?" As above, since metformin might not be the relevant first line treatment for all patients and the efficacy and safety profiles of established treatments are well known, there is sufficient scientific data for having other established first line agents as the comparator in monotherapy studies.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		If the objective of a trial is only to assess the treatment for use as monotherapy with respect to glucose lowering effect a randomised placebo-controlled trial is regarded as sufficient. As metformin, in the future, is not regarded as the standard of care/established therapy for all patients with type 2 diabetes who would benefit for initiation of glucose lowering treatment, a requirement for a head-to-head comparison to metformin to obtain a monotherapy indication is difficult to justify. However, head-to-head trials comparing the treatment with monotherapy indication will likely be done to assess potential treatment differences both in treatment naïve patients and as add-on to other background treatment, but this should not be regarded as a requirement for approval. **Proposed changes:** Suggest deleting the specific requirement for a head-to-head trial with metformin for a monotherapy indication. Instead mention one or a few other established first line agents (than metformin).	
108-111	1	3) With respect to other benefits; Should a product have to show a documented effect on diabetes complication, i.e. on micro- and/or macrovascular endpoints to support an unrestricted monotherapy indication? Can other benefits, even if unrelated to diabetes control, e.g. lowering of body weight, justify a first line treatment?" **Comments:** Non-glycaemic benefits (either effects on co-morbidities or on long-term clinical outcomes) are relevant to decision-making for individual patients, however they should not be the basis for constraining the monotherapy indication as being restricted or unrestricted.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Considering the particular situation of monotherapy indication, to demonstrate benefit on diabetes complications might not be feasible. However, added clinical benefit such as weight loss, or even prominent benefit in QoL may be sufficient to support monotherapy treatment for certain populations. Furthermore, as HbA_{1c} is a valid and accepted biomarker and the amount of evidence which supports that improvement in HbA_{1c} is linked to reduction of both micro- and macrovascular complications it should not be a requirement to demonstrate beneficial effects on long-term diabetes complications. If such data are required, it will have large implications for the duration of trials and number of participants in the development program which will have impact on the development of new treatments of type 2 diabetes. In addition, it is unclear why such data would be required for monotherapy and not for combination therapies, the latter being a segment including more patients with complications. The use of other biomarkers is regarded as upsides but not as such the main objective/endpoint for the treatment of type 2 diabetes. **Proposed changes:** Delete the requirement regarding a documented beneficial effect on diabetes long-term complications for a monotherapy indication.	
112-115	1	"4) If benefits on micro- and/or macrovascular endpoints are no longer required; would this mean that sponsors will perform fewer studies (e.g. studies to document effects on such endpoints)……?" **Comments:** As benefits on micro- and/or macrovascular complications can be included in the Summary of Products Characteristics and have implications for the general	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		usability/attractiveness seen both from a patient, prescriber and payer point of view sponsors would most likely have an interest in conducting such studies in the post-approval phase, if not done as part of the IIIa/IIIb development program. This interest is further supported by the implication of changes in major treatment guidelines such as ADA's Standards of Medical Care in diabetes. As per EMA's "Reflection paper on assessment of cardiovascular safety profile of medicinal products", the evaluation of potential cardiovascular benefits associated with medicinal products intended for the treatment of diabetes with a CVOT is not required. Ultimately, the mechanism of action and profile of a new agent will guide the need for larger outcome studies and the number of clinical trials. In some cases, proof of CV safety may still be needed for new mechanisms of action. If no CV safety signal has been identified during the early clinical and preclinical programs, generation of long-term data on CV effects and / or microvascular parameters could be generated through pooled analysis and post approval studies, instead of conducting a dedicated pre-approval CVOT. Based on existing evidence sponsors strive to show benefit beyond improvement in HbA1c, which may include post approval studies. In general, the impetus to conduct additional studies (not only CVOT/longer-term studies) to support a claim remains the same. Such studies are still of scientific and clinical importance to support appropriate positioning of drugs in a landscape of individualised therapy. **Proposed changes:** In line with the EMA "Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes" Rev. 2 draft of 29 January 2018 there should be no requirements for a dedicated cardiovascular outcome trial	to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		for new products indicated for treatment of type 2 diabetes, if the development programme (i.e., pre-clinical, phase II and phase III data) showed no suspicion of increased CV risks. This is in accordance with both the EMA reflection paper and the pre-approval recommendations in FDA's guideline (USFDA Guidance for Industry Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes Dec 2008). Furthermore, the choice of comparator for CVOTs (placebo or an active comparator) is beyond the scope of the diabetes guideline The same should be the case for microvascular complications. Micro- and/or macrovascular risks should be assessed based on the pre-clinical studies and phase II and III confirmatory studies. If a signal for increased risk is seen, then studies should be considered. In line with FDA, it is proposed that a separate micro- and/or macrovascular indication is granted when a diabetes drug has shown such benefit. The current EMA approach referencing data in other sections does not provide a clear message to prescribers and should be modified in line with the approach taken by FDA where the indication is granted when a beneficial effect has been demonstrated.	
146-156	1	**Comments:** The preferred choice is Option 1, to have a more general indication wording with reference to section 5.1 showing which studies have been completed. This would provide some flexibility and would give the physicians opportunity to align practice with clinical guidelines, as well as the studies that have been conducted as described in section 5.1. This wording would include, but not explicitly state, initial combination therapy. The rationale for this option would be that if a certain combination has been studied in a later line of treatment and been found efficacious and with an acceptable safety profile, it could also be used as initial therapy if	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		supported by treatment algorithms developed by learned societies or if a prescriber finds a specific patient eligible for such a treatment (this treatment strategy would be in line with some statements in ref. 2.) Option 1 is also preferred as the benefit/risk profile would at least be the same for a treatment naïve subject as the risk would likely not increase as type 2 diabetes is progressive and patients in general are regarded as more fragile if the disease has progressed. **Proposed changes:** Change the claim to "in combination with other glucose lowering agents" – with a reference to section 5.1 of the SmPC and highlight that this includes initial treatment when justified.	The guideline will not discuss first line combination treatment. This is instead reflected in the FDC guideline. The add on combination wording will not be changed
157-162	1	"Option 2" If a sponsor aims for the indication "in combination with other glucose lowering agents", or a specific initial combination therapy indication, studies in previously (medically) untreated patients would need to be included in the data package. If not, the indication would be "add-on to other glucose lowering agents". The outcome measures and duration of such studies would need further consideration, and proposals from external stakeholders are welcomed." **Comments:** Please refer to comment for Option 1 above.	
164-179	1	**Comments:** We support that the text in line 166-175 taken from section **4.4.4.4. Combinations with insulin** in the "Guideline on clinical investigation of	The section has been shortened

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		medicinal products in the treatment or prevention of diabetes" Rev. 2 draft of 29 January 2018 can be deleted, since it can be covered by the section "Add-on (or combination therapy)". As insulin has no maximal tolerated (might not be known in individual patients) or recommended dose it would be relevant for such patient groups to use a wording regarded as a stable and maximal effective and tolerated dose. **Proposed changes (if any):** Delete the two paragraphs (line 166-175) as suggested. However, as insulin has no maximal tolerated (might not be known in individual patients) or recommended dose it would be relevant for such patient groups to revise wording to e.g. stable and maximal effe ctive and tolerated dose in the "Add-on (or combination therapy)" section And in the "Add-on (or combination therapy)" section the specific studies needed to quantify the HbA_{1c} reduction and provide guidance on the additional expected benefits provided by the new compound when added to insulin or when insulin is added to the new compound should be described.	
Line 104	7	**Comment:** In light of new treatment options with additional benefit beyond HbA1c lowering, the strict focus on metformin as the comparator for a monotherapy-claim should be removed. **Proposed change (if any):** Instead of requiring metformin, the guideline should require an active comparator with established benefit as a mono-therapy or with a recommendation in a treatment guideline.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 66-67	8	**Comment:** Please clarify what is meant by other stakeholders in the sentence "results from such a study would be of value for other stakeholders"	HTAs and similar stakeholders
Line 104	8	**Comment:** "*Is it still relevant to reflect the first line status of metformin in the therapeutic indication?*" No, given the advances with e.g. SGLT2i and the well-tolerated profile of this class the first-line status of metformin need not be reflected. While metformin was once the first line gold standard and other diabetes drugs only considered first line in case of metformin intolerance, the development of new drugs as well as the treatment paradigms have moved on. Newer products (SGLT2, GLP-1) have now become established treatments and allow prescribers possibilities to individualise the treatment approaches to suit the patient characteristics. Removing the reflection of first line status for metformin in the indication will allow the guidance and the indication wording to reflect the evolving treatment paradigm going forward. **Proposed change (if any):** Remove reflection of first line status of metformin in the therapeutic indication.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
Lines 105-107	8	**Comment:** "*With respect to glucose lowering effect; is it still of value/necessary to require a direct comparison to metformin or would a comparison to another approved treatment or even a comparison to placebo be enough to ensure a satisfactory glucose lowering effect?*"	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		A direct comparison to metformin should not be required, and flexibility should be given with regards to how satisfactory glucose lowering effect can be demonstrated, including vs placebo (for short term studies, and provided this is possible from an ethical point of view). **Proposed change (if any):** Remove requirement for direct comparison to metformin.	to be shown if such claims are proposed in the SmPC.
Lines 108-111	8	**Comment:** "*With respect to other benefits; Should a product have to show a documented effect on diabetes complication, i.e. on micro- and/or macrovascular endpoints to support an unrestricted monotherapy indication? Can other benefits, even if unrelated to diabetes control, e.g. lowering of body weight, justify a first line treatment?*" Documented effect on micro- and/or macro-vascular endpoints should not be required to support an unrestricted monotherapy diabetes indication. The optimum endpoints to study in order to support other benefit claims (e.g. weight control, micro-/macro-vascular outcome, chronic heart failure or chronic kidney diseases) should be determined based on the profile of the product. Furthermore, rather than requiring a specific outcomes study, such as a cardiovascular outcomes trial to demonstrate safety, a more conventional safety collection approach would be possible. **Proposed change (if any):** Revise the wording in the guideline to allow a broader spectrum of benefits that would support first line treatment, allowing alignment with the evolving treatment paradigm, earlier onset of treatment etc.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 112-115	8	**Comment:** "*If benefits on micro- and/or macrovascular endpoints are no longer required; would this mean that sponsors will perform fewer studies (e.g. studies to document effects on such endpoints)? Considering the results of performed CVOTs, is there still equipoise to perform placebo-controlled CVOTs?*" While it may be that removing the requirement for micro- and/or macro-vascular endpoints could lead to fewer or smaller studies, it should also be considered that since the introduction of the requirement for CVOTs, other potential benefits may not have been explored due to the high cost and effort associated with CVOT studies. Fortuitously, both SGLT2i and GLP-1 have shown CV benefits, but it is debatable whether these were foreseeable at the time of study inception and appear not linked to their glycaemic effect. A prescriptive requirement for CVOTs (MACE endpoint) may hinder exploration of other benefits. Removing the requirement for a CVOT, as it stands today, is not likely to curb the generation of relevant outcomes data. In the current environment with many medicines having shown endpoint benefits not only in the cardiovascular, but also the renal space, for any new diabetes drug to be competitive and play a role in the treatment of T2DM, it would need to demonstrate other benefits than only HbA1c reduction. **Proposed change (if any):** For a regulatory approval of a diabetes indication a CVOT should not be required. Data to support additional benefits should be generated as relevant.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
Lines 146-156	8	**Comment:** While studies of combination therapy in previously (medically) untreated patients may be less likely to be performed as pointed out in the reflection paper, Option 1 is still preferred. This option allows individualized treatment	The guideline will not discuss first line combination treatment. This is instead reflected in the FDC guideline.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and prescriber flexibility as treatment targets, no longer solely focused on glycaemic control, continue to evolve. Relevant study details would be included in 5.1 and provide the information necessary to understand the underlying data. There are also clinical study implications with regards to studying treatment naive patients that needs to be taken into consideration. With more and better tolerated treatments available it will be increasingly challenging to find treatment naive patients, and where these remain, rescue treatment impedes the ability to interpret results in these often poorly controlled naive patients. Furthermore, if the medication works in combination with other medicines, it seems unreasonable to assume that they would not work as initial monotherapy. **Proposed change (if any):** Implement Option 1 in guideline.	The add on combination wording will not be changed
	8	**Comment:** We agree that the specific section on combination with insulin can be deleted and covered by the section "Add on (or combination therapy)". However, we believe that if there is still to be any guidance on add on studies with insulin, there should not be a requirement that treatment groups be balanced with regards to insulin regimens. While appealing on the surface, balancing treatment groups with regards to the types of insulin used poses an additional challenge by introducing a further stratification factor, even ignoring that there are so many regimens and types of insulin that the task would be daunting. It is already in the Applicant's interest to ensure a balance between study arms. In reality, there is a large national or regional component to how and which insulins are used, and it is anticipated that this would be handled by	The guideline will not discuss first line combination treatment. This is instead reflected in the FDC guideline. The add on combination wording will not be changed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		other stratification factors rather than mandating one for types of insulin. Each stratification factor increases complexity in the study. It should also be noted that the potential insulin sparing effect of a combination treatment may be missed if the recommendation to leave background medication unchanged in the combination therapy section (bullet (iii), see line 133-135 in this reflection paper) would also apply to insulin. It should be possible to down titrate insulin in the event that a novel agent has significant insulin sensitizing properties. **Proposed change (if any):** Specific section on combination with insulin can be deleted and covered by the section "Add on (or combination therapy)", taking into account the comments above.	
Lines 49-50	9	**Comment:** A placebo-controlled trial is an exception that is only acceptable when no standard-of-care treatment exists. This may be the case if the new drug is being evaluated as an add-on to an optimised therapy. But even in this situation, the new drug must be evaluated on the basis of clinical outcomes that matter to patients, in particular the clinical complications of type 2 diabetes, not solely on the basis of a surrogate endpoint such as HbA1c level. The thiazolidinediones (also known as glitazones) are an example of drugs that reduce HbA1c level but increase the risk of heart failure and myocardial infarction (*4*). Hence, the importance of evaluating drugs on the basis of clinical outcomes. **Proposed change (if any):**	HbA1c is the preferred primary endpoint, not the ones mentioned in this comment.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"*Superiority of the new agent over placebo, based on clinical endpoints such as mortality, micro- or macrovascular complications of type 2 diabetes, when added to an established background therapy, which represents standard of care in the studied population"*	
Lines 51-53	9	**Comment:** We welcome the requirement for at least one trial versus standard of care. However, in order to improve patient care, this trial should be designed to evaluate the new drug's potential superiority over standard of care, rather than just its "non-inferiority". In addition, in order to provide high-quality evidence of one drug's superiority over another, at least two clinical trials with consistent results are required, to minimise the effects associated with sampling in each trial. **Proposed change (if any):** "~~Non-Inferiority~~ *Superiority of the new agent over an established active comparator (in a monotherapy or add-on study depending on the intended indication) representing standard of care. The submission of at least ~~one~~ two active controlled studies is recommended ~~to be submitted~~ with the marketing authorisation application."*	Superiority over existing therapies is not a requirement for approval.
Lines 54-55	9	**Comment:** The proposed minimum trial durations (6 and 12 months) seem too short to evaluate the effects of a glucose-lowering drug on the clinical complications of type 2 diabetes, including its long-term complications. The time to onset of the complications of type 2 diabetes varies between patients and depends on a number of risk factors. It often takes several years. Rather than specifying a minimum trial duration, it would be better to require trials that are long	There is not requirement to show a beneficial effect on complications.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		enough to properly evaluate the new drug on the basis of the clinical complications of type 2 diabetes, with a high probability to demonstrate a statistically significant difference on the clinical outcomes between each group. **Proposed change (if any):** *Trial duration should be long enough to properly assess the new agent on the basis of the clinical complications of type 2 diabetes.* ~~*Confirmatory studies are typically 6 months in duration but at least one trial, preferably active controlled, should demonstrate maintenance of effect over at least 12 months.*~~	
Line 60-61	9	**Comment:** It is unacceptable that the European Medicines Agency declares it is not essential to conduct a trial versus standard of care or an already widely used treatment in order to obtain marketing authorisation, and that it considers placebo-controlled trials to be the gold standard. In a clinical situation in which a variety of drugs is already available, a placebo-controlled trial cannot show whether the new drug constitutes a therapeutic advance. And the patients in the placebo group are not receiving the best available care.	Superiority over existing therapies is not a requirement for approval.
Line 81-83	9	**Comment:** *Metformin* is usually the better choice for first-line drug treatment when selecting a glucose-lowering drug for a patient with type 2 diabetes, due to the comparative data available on its efficacy, based on clinical outcomes, and on its adverse effects profile (*1*). The fact that a new drug markedly reduces blood glucose levels is no reason to avoid conducting a trial versus *metformin* with clinical endpoints.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): If an indication for first line (unrestricted) monotherapy is intended, a monotherapy study comparing *the test drug to metformin is* ~~usually~~ *needed* ~~unless the robustness and magnitude of the glucose lowering effect of the test drug is very convincing~~. *In addition, beneficial effects on micro- and/or macrovascular endpoints and a well characterised safety profile (including data on long-term safety)* *versus metformin must* *be documented before a first-line monotherapy indication would be considered approvable.*	
Line 104	9	**Comment:** Yes, *metformin* is the first-line glucose-lowering drug for type 2 diabetes. The other drugs authorised, such as GLP-1 agonists, are at best to be considered when *metformin* is deemed insufficiently effective or its adverse effects too severe (*1*).	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
Lines 105-106	9	**Comment:** Glucose-lowering drugs should not be evaluated solely on the basis of surrogate endpoints such as HbA1c. An evaluation based on clinical outcomes, such as the clinical complications of type 2 diabetes must be the rule. When a drug is intended for use as monotherapy, drug regulatory agencies should require a comparison versus *metformin.*	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 108-111	9	**Comment:** Yes, any new drug intended as a treatment for type 2 diabetes should be evaluated using clinical endpoints, such as the micro- or macrovascular complications of diabetes. Other potential benefits unrelated to diabetes control, such as weight loss, are insufficient to justify marketing authorisation for use in patients with type 2 diabetes.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
Lines 112-115	9	**Comment:** The first question is irrelevant, because any new drug intended for the treatment of type 2 diabetes should be evaluated using clinical endpoints such as its ability to reduce the micro- or macrovascular complications of type 2 diabetes. In addition, as some glucose-lowering drugs (including *metformin*) appear to reduce mortality or the incidence of the clinical complications of diabetes, it is unethical to conduct long-term placebo-controlled clinical trials in patients with type 2 diabetes (*1*). An exception could perhaps be made for trials aiming to evaluate the addition of a new drug to already optimised therapy.	Placebo controlled trials are the gold standard for evaluation of efficacy. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
Line 123	9	**Comment:** It is important that the EMA specifies which exceptional circumstances would make a placebo-controlled trial acceptable and which circumstances would require an active controlled trial. **Proposed change (if any):**	Placebo controlled trials are the gold standard for evaluation of efficacy. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Add-on studies should be placebo-controlled <u>if the new agent is added to the standard treatment, and</u> active controlled <u>if the new agent replaces another drug in standard treatment</u>.	
Lines 147-162	9	**Comment:** A combination of drugs as first-line therapy for type 2 diabetes would only be acceptable in exceptional cases, due to the additional adverse effects to which patients would be exposed. The main aims of treatment are to prevent the clinical complications of type 2 diabetes, including its long-term complications. It is rarely useful for patients to lower blood glucose rapidly. *Metformin* monotherapy is generally the most prudent choice as first-line drug treatment, potentially offering monotherapy with a different drug or combination therapy subsequently if *metformin* alone is insufficiently effective. The prudent choice in initial therapy is to use monotherapy first. As first-line drug treatment, glucose-lowering drugs should not be authorised in combination therapy.	The guideline will not discuss first line combination treatment. This is instead reflected in the FDC guideline.
Lines 54-55	10	**Comment:** In our opinion, in confirmatory trials, use of active control should be a necessary requirement and not just a preferable alternative option to placebo, for ethical reasons (an abundance of established glucose lowering agents is available) and also to increase applicability and relevance of trials findings in clinical practice. **Proposed change (if any):** Keep text in third bullet	Placebo controlled trials are the gold standard for evaluation of efficacy.
Lines 69-80	10	**Comment:** In our opinion, exposing a patient with newly diagnosed type 2 diabetes to hyperglycaemia should not be the case. We have evidence that effective antihyperglycemic treatment from the diagnosis of diabetes reduces	Placebo controlled trials are the gold standard for evaluation of efficacy.

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		the risk of adverse sequelae after years of disease duration. Studies with an active comparator should be preferred.	
Line 75	10	**Comment:** Perhaps it would be more rational and ethical to suggest a lower threshold for baseline HbA1c (e.g. 8%) for monotherapy placebo-controlled trials.	This is reflected in the guideline
Line 104	10	**Comment:** For specific groups of patients like patients with type 2 diabetes and increased cardiovascular risk or presence of CKD or heart failure for whom SGLT2 inhibitors or GLP-1 RAs are now indicated as first line options irrespective of background use of metformin (and irrespective of baseline HbA1c) we think it is not relevant anymore to consider and reflect metformin as the only first line option. On the other hand, for other patients without aforementioned comorbidities treated for hyperglycaemia, it is still relevant to consider and reflect metformin as the first line option.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments.
	10	**Comment:** In our opinion, yes regarding the results of the UKPDS	No outcome
Lines 105-107	10	**Comment:** Related to the previous comment, we think that it is reasonable and clinically relevant to include additional agents other than metformin as acceptable comparators in monotherapy trials, based on suggested first line options; e.g. an SGLT2 inhibitor in patients with t2dm and CKD or an SGLT2 inhibitor or a GLP-1 RA for patients with established atherosclerotic disease. Related to the comment for lines 54-55, we advocate the use of active comparator, and not placebo, in confirmatory trials.	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments.
Line 107	10	**Comment:** comparison with placebo - not	Placebo controlled trials are the gold standard for evaluation of efficacy (if ethical).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Lines 108-111	10	**Comment:** In our opinion, other benefits, e.g. lowering of body weight, justify the first-line treatment of type 2 DM, if simultaneously leads to improve glycaemia.	Acknowledged
Lines 108-109	10	**Comment:** Of course documented benefits for diabetes complications are desirable but the demonstration of such effects takes a long time. We do not think there should be a requirement to demonstrate such effects for initial approval (see also comment for 112-115).	Metformin is no longer required as comparator as other substances are also recognized as established, first line treatments. Requirements to show effectiveness against complications is not needed for an indication for the treatment of type 2 diabetes but has to be shown if such claims are proposed in the SmPC.
Lines 110-111	10	Instead of documented beneficial effect, requirement for no harmful effect would be inserted (no worsening albuminuria or retinopathy, for example) **Comment:** With regard to benefits not directly related to glucose reduction, such as body weight reduction (lines 110-111), we believe that these effects alone do not justify an indication of a new agent as an antidiabetic medication, but they do merit consideration as supplementary benefits to the primary effect (glucose lowering); for example, an agent may be prioritised over other agents with a similar glucose lowering effect, if it has additional benefits such as body weight reduction. Again, this issue is also relevant to add-on indications and not only to monotherapy first line indication.	Agreed
Lines 112-115	10	**Comment:** CVOT results may not be required for initial approval of new agents, but our suggestion is that initial indication approval should be **conditional**, meaning that an indication can be given under the condition that	Diabetes drugs are in general not fulfilling the requirements for CMA

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		the manufacturer is already conducting an ongoing CVOT for the new agent. By doing so, the initial indication approval of a new agent can be revoked in case that CVOT data (even preliminary) suggest an unfavourable safety profile of said agent. Regarding use of placebo, we believe that CVOTs should now be active controlled versus an approved agent with proven CV benefits, as is the case with the ongoing CVOT with tirzepatide (SURPAS-CVOT) which is versus dulaglutide.	
Line 123	10	**Comment:** From an ethical perspective, we believe that use of placebo as a control should be restricted only to isolate the genuine glucose lowering effect and short-term safety of a new agent and for that just a single short-term placebo trial would suffice.	In line with the guideline
Line 123	10	**Comment:** In our opinion, placebo trials should be limited.	Only for short term in newly diagnosed patients
Lines 146-162	10	**Comment:** Option 2 more reasonable; In our opinion, it is better to distinguish an indication as "add-on to pre-existing glucose lowering therapy" from an indication as "initial combination therapy", even though both belong to the broader indication "in combination with other glucose lowering agents".	The guideline will not discuss first line combination treatment. This is instead reflected in the FDC guideline. The add on combination wording will not be changed
Lines 178-179	10	**Comment:** Agree that there is no clinically practical reason for insulin to merit a special section.	Agreed
	10	**Comment:** We were wondering if it would be appropriate (and relevant) to this document to focus not only on the components of the PICO question of RCTs but also on the analysis, and for CHMP to reflect/provide guidance on the use of estimands, aligning (?) itself with ICH/FDA that issued a relevant	This is included in the guideline

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		document (*E9(R1) STATISTICAL PRINCIPLES FOR CLINICAL TRIALS: ADDENDUM: ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS, May 2021 Update 1*)	
Lines 178-179	10	**Comment:** Agree with the proposition of suggested changes regarding combination therapy with insulin.	Agreed