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Overview of comments received on "Guideline on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease of the lower extremities"

(EMA/CHMP/EMA/CHMP/464798/2024 Rev. 2)

Name of organisation or individual	General or Specific comment	Line from (line nr. or 0 for general comment)	Line to (line nr. or 0 for general comment)2	Comment and rationale (to go to next line within the same cell use Alt + Enter)	Proposed changes / recommendation (if applicable - to be used if you want to propose specific text changes)	Outcome (To be completed by the Agency)
Novo Nordisk A/S	Specific	212-224		We appreciate the clarity on recommended testing. It would be useful to clarify also if 2 different methods of testing in the same trial would be considered appropriate, and the recommended interval between them (e.g. treadmill test plus 6MWT).		New specifications included in the text as follows (page 8): *The 6MWD and treadmill test are not interchangeable and the choice between the two methodologies should take into account, among other parameters, the studied population in terms of disease stage and concomitant CV conditions, as well as accessibility to the different rehabilitation programs (either supervised treadmill or home-based exercise), especially in global trials, which can all distinctly affect the measured outcomes (new refs: McDermott et al, J Vasc Surgery 2020;71(3):988-1001; and A Clinical European Consensus Document on PAD training 2024, Eur J Vasc Endovasc Surg (2024) 67, 373e392). Should the 6MWD and treadmill test be proposed for efficacy assessment in the same trial, results from both measures are expected to be consistent with a treatment-dependent functional improvement.*
Novo Nordisk A/S	Specific	227-229		ICD is recommended as primary endpoint. However, we would suggest to add the detail that for diabetes populations it may be preferable to use ACD also for the constant load test, as the presence of neuropathy-associated symptomatology may influence the pain perception (as mentioned on page 5, lines 109-110)	For trials performed in a population with diabetes, the use of ACD as primary endpoint may be preferable due to the probable presence of neuropathy-associated symptomatology that may influence pain erception.	No changes: the current description of the ICD and ACD parameters specifies their relative subjectivity (line 240) and reproducibility (line 244) which account for the differences across patient subpopulations, including diabetics, that should be taken into consideration in the choice of clinical endpoints.
Novo Nordisk A/S	Specific	262-265		We would appreciate some guidance on adequate QoL questionnaires applicable to a PAD population, for both general HRQoL and PAD specific QoL.		New specifications included in the text as follows (page 9): *Clinical studies to support regulatory submissions are encouraged to use disease-specific carefully validated tools. For generic considerations, reference is made to the Reflection paper on the regulatory guidance for the use of health related quality of life (HRQL) measures in the evaluation of medicinal products (EMEA/CHMP/EWP/139391/2004)*
Novo Nordisk A/S	Specific	226-242		We would appreciate guidance on responder evaluation in trials focused on Intermittent Claudication for improvement in walking distance. Interpretation of clinical relevance is not clarified. Suggest to clarify that clinical relevance may be determined through e.g. anchor based methods for determining responder rates. Otherwise, there is no defined standard to what is relevant as improvement in walking distance or time, and this may vary greatly in different populations /severity levels.		No changes: the guidance currently recommends that "*The minimal clinically important difference (MCID) that is intended to be used in the inference of efficacy of treatment requires to be pre-specified in the study protocol and is expected to be justified and relevant to the specific targeted population* (lines 251-253).
Novo Nordisk A/S	Specific	276-277		It is recommended that only major amputations should be counted. However, beyond their uncertain impact on QoL it was shown that minor amputations are associated with risk of major amputations and death and should be considered as a pivotal event for the patients (Birmpili P, Li Q, Johal AS, Atkins E, Waton S, Chetter I, Boyle JR, Pherwani AD, Cromwell DA. Outcomes after minor lower limb amputation for peripheral arterial disease and diabetes: population-based cohort study. Br J Surg. 2023 Jul 17;110(8):958-965. doi: 10.1093/bjs/znad134. PMID: 37216910; PMCID: PMC10361679. and Kaissar Yammine, Fady Hayek, Chahine Assi, A meta-analysis of mortality after minor amputation among patients with diabetes and/or peripheral vascular disease, Journal of Vascular Surgery, Volume 72, Issue 6, 2020, Pages 2197-2207, ISSN 0741-5214, https://doi.org/10.1016/j.jvs. 2020.07.086. (https://www.sciencedirect.com/science /article/pii/S0741521420318760). A mention of minor amputations in prevention trials would be appreciated.		No changes: major amputations provide a more robust endpoint than minor amputations, since etiologies can distribute with a different pattern in major and minor amputations (i.e. infections alone, ischaemia alone, multifactorial; Nicholas Govsyeyev et al. J Vasc Surg 2022;75(2):660-670) adding complexity to data interpretation and potentially biasing the analysis of ischaemia-related major events.
Novo Nordisk A/S	Specific	328-329		It would be appreciated to add recommendations on methods for determining clinical relevance (e.g. anchor-based, SD-based, etc.) This seems to be little known and understood, including among drug evaluators.		No changes:general principles in statistical analysis apply, with reference made to available metodhology guidance (line 329). For definition of clinical relevance, see comments above.

Novo Nordisk A/S	Specific	551-563		We appreciate the importance of having recommendations for vulnerable populations. For the specific PAD evaluation, we consider that additional recommendations for diabetes population would be needed, considering not only the high risk of coexistence, but also the specific neuropathy associated symptomatology (pain perceptiuon), risk of diabetic foot ulcers leading to amputations and the specific localisation of the disease at the levl of the small vessels below the knww. These may require a different approach in both functional and prevention trials.		No changes: no diabetes-specific requirements apply for efficacy evaluation other than a recommended stratification by diabetic status in confirmatory trials (lines 452, 511, 629).