Comment form for the factual accuracy check by the HTD (Saluda Medical) on JCAMD002 evoke

The objective of this reviewer form is to standardise the process of the factual accuracy check of the Joint Clinical Assessment (JCA). The final version of the JCAMD002 on evoke was open for a factual accuracy check by the health technology developer (HTD) Saldua medical between 19/06/2023 and 23/06/2023.

Comments received from: HTD, Saluda, Medical

All received comments are formally responded in this combined document, to be published on the EUnetHTA website, name of organisation/institution (or individual names of the reviewers/affiliations) disclosed.

Page number *Insert 'general' if your comment relates to the whole document*	**Line/ section number**	**Comment and suggestion for rewording** *Please insert each new comment in a new row.*	**Character of comment** • 'major'[a]=1 • 'minor'[b]=2 • 'linguistic'[c]=3 *Please indicate your choice by writing the according number in this field, e.g. for major choose "1".*	**Authoring team response**
13	206-8 218-9	As mentioned in the HTD submission dossier, "PSPS is a recent definition that includes both Type 1 and Type 2." Without the differentiation between Type 1 and Type 2, the term PSPS refers to "the full adult patient population with chronic, intractable pain of the trunk and/or limbs" and not a subpopulation. In this particular case, the population with chronic, intractable pain of the trunk and/or limbs would be the subpopulation of "chronic intractable pain". PSPS-Type 1 and PSPS-Type 2 would be subpopulations of PSPS (i.e., chronic, intractable pain of the trunk and/or limbs).	1	It was considered that the definition of the full patient population (chronic intractable pain) consisted of not only neuropathic pain. As a result of the PICO consolidation process, PSPS was defined as a subpopulation of chronic intractable pain because PSPS is a type of neuropathic pain.
15	Table 3 "Description of the device including its constituents"	For eCLS and CLS it says "…which delivers automatic or manually controlled therapy". This is not factually accurate, and it would be more correct to use the text from the dossier which states "The Evoke System may deliver 1) open-loop stimulation, equivalent to the mechanism used by other commercially available SCS systems but with the	1	Thank you for your explanation. In this row the constituents are described one by one very briefly. The quoted wording is from the Evoke® SCS System User Manual D102706 Rev 2.00 that was a piece of the supporting documents to the HTD submission dossier. Additionally, the explanation you suggest is already

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		additional feature to measure ECAPs; or 2) ECAP-controlled closed-loop stimulation, where the stimulation amplitude is automatically adjusted in real-time to minimize the difference between the measured ECAP and the target ECAP to deliver consistent spinal cord activation at the target level."		presented in the same table in row "mode of action" *(The Evoke System delivers either 1) open-loop stimulation; or 2) ECAP-controlled closed-loop stimulation, where the stimulation amplitude is automatically adjusted in real-time to minimise the difference between the measured ECAP and the target ECAP to deliver consistent spinal cord activation at the target level.)*
15	Table 3 "Mode of action"	"The stimulation program(s), and thereby the stimulation mode, is determined by the treating clinician." The stimulation program(s) and mode are not determined by the treating clinician alone, this is always done with patient feedback. Please correct to "…by the treating clinician with patient feedback."	1	Thank you for the suggestion, we corrected it.
18	Table 4	Please remove the internal document numbers included after each manual (D10XXXX). These were inadvertently included.	2	Thank you, we removed these document numbers.
19	Table 4	Please change the date of expected BSI review of MDR application from "December 2023" to "May 2024".	2	Thank you, we updated the date.
23	322-3	"However, the Avalon study is presented for the safety outcomes in Section 4.4. as the study provides longer follow-up data on safety than the RCT and some safety endpoints not reported in the RCT." This is not factually correct. Although not available in the CSR for the Evoke RCT, 24-month safety data from the Evoke RCT has been	1	The 24-month results of the RCT have not been presented because the CSR was not provided and thus we were not able to check and validate the results from the publication. We added a footnote to explain this in the JCA report.

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		published (ref #12 in JCA report) and provided in the HTD dossier.		
24	Table 8	"The study is a systematic review …" "…in this systematic review …" The reference for the study provided by the HTD in their dossier for this study was reference #41 "Duarte RV, Soliday N, Leitner A, Taylor RS. Health-Related Quality of Life Associated With Pain Health States in Spinal Cord Stimulation for Chronic Neuropathic Pain. Neuromodulation Technol Neural Interface. 2021 Jan 1;24(1):142–9." The study is not a systematic review but an evaluation of HRQoL according to different pain health states. Ref #14 in the JCA report is for a study not related with the Evoke SCS system.	2	Thank you, we used the wrong reference. We corrected the reference to the one you mention and updated the reason for exclusion.
25	Table 9	"Only secondary endpoints controlled for multiplicity" but we are unclear as to why the following outcomes were dismissed: • incidence of ≥80% reduction in VAS overall trunk and limb pain at 12 months (CSR page 290) • incidence of ≥50% reduction in VAS back pain at 12 months (CSR page 290)	1	Thank you, we added these outcomes in Table 9.
26	Table 9	Although not requested by EUnetHTA 21 in the PICO for this assessment, the HTD provided outcome data in their submission dossier for Neurophysiological data (Device utilisation, Mode ECAP, Percent time in therapeutic	1	Thank you for your comment. This is outside the scope of a factual accuracy check of the JCA report.

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		window, Neural accuracy, Conduction velocity). Although not requested, the HTD consider this objective data to be of paramount importance when evaluating neurostimulation devices.		
26	Table 9	"[h] Not prespecified in the protocol but reported in the submission dossier (the CSR reported data for a lower number of patients than in the submission dossier)." Important to clarify the reason for the lower number of patients in the CSR; the CSR is for the 12-month analysis, only patients that had completed their 24-month visit at the time the report was produced were included in the CSR.	1	Thank you, we added the explanation you provided.
28	366-73	"However, the technical characteristics of the open-loop stimulation mode of Evoke SCS System are insufficiently described to be able to conclude if the stimulation mode belongs to the latest generation of open-loop SCS systems." This is factually inaccurate. SCS stimulation that does not use closed-loop is open-loop stimulation (see for example Katz et al 2021 Table 1 and section 4 [ref #14 in the submission dossier] "All SCS therapies are challenged by the ever-changing distance between the electrode and the spinal cord with patient movement, the cardiorespiratory cycle, and coughing,[68] which might contribute to variability in clinical outcomes.[164] For this reason, investigators developed "closed loop," which	1	Thank you for your comment. This is outside the scope of a factual accuracy check of the JCA report.

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		measures the evoked compound action potential from the spinal cord after each pulse and automatically adjusts the strength of the next pulse to maintain a specified evoked compound action potential size.[101,128,129] The fact that ECAPs can be measured in open-loop to adjust stimulation parameters provides an advantage over other open-loop systems, none of which have this capability. Hence why Evoke using open-loop stimulation can be considered to belong to the latest generation of open-loop SCS systems.		
28	Table 13	Evoke open-loop SCS median age should be 57 and not 56 (see CSR page 48)	2	Thank you, we corrected it.
31	402-3	"The outcome "responder rate measured by global pain relief of ≥50% vs baseline at 6 months minimum" was not reported as such in the CSR." This is factually inaccurate, ≥50% improvement vs baseline in overall trunk and limb pain scores at 6 and 12 months is reported in page 85 of the CSR. This also has repercussions in inaccuracy for the subsequent text in lines 403-7. Although we appreciate it may be preferable to use the primary composite outcome for the reasons stated by the assessors, the information in the report as it stands is inaccurate. The reason why the results are the same for the primary endpoint and ≥50% improvement vs baseline in overall trunk and limb pain is	1	Thank you for the clarification. We edited the paragraph accordingly.

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		because the 50% responder rates and composite primary endpoint (with medication component) could be the same if the medication failures were the same as the patients who had <50% pain reduction. As reported in Table 10.2 (page 64) of the CSR, the reasons for primary endpoint failure of <50% overall trunk and limb pain relief at follow-up visit and increase in baseline pain medications within 4 weeks of the follow-up visit were not mutually exclusive.		
31	409-11	"It is not clearly stated that the 12-month assessment would look at the 4 weeks of the 3 months or the 4 weeks of the 12 months." This may have been a wording issue in the protocol and CSR but although not clearly stated, a 12-month assessment relying on a 3-month endpoint does not make sense. The 12-month assessment considered of course the 4 weeks before that visit and not that period before the 3-month visit. Please also note that one of the reasons for Primary Endpoint Failures clearly states "Increase in baseline pain medications within 4 weeks of the follow-up visit".	3	Thank you for the clarification. We edited the paragraph and added that the HTD clarified this point.
31	Table 14 Pain	"pain was assessed" is repeated	3	Thank you, we corrected it.
40	Table 20	For "Muscle spasm or muscle cramp", Evoke closed-loop SCS should be N=2, 2/67 (3) (CSR page 265)	2	The reported data is correct. It is from the CSR, table 11.5 "Summary of Procedure and/or Device-related AEs".

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46	Table 27 All outcomes / Applicability	Same comment as above for page 28 regarding applicability of comparator used.	1	Thank you for your comment. Comments about the applicability are considered outside the scope of the factual accuracy check of the JCA report.

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47	Table 27 Overall endpoint success / Applicability	"The outcome requested in PICO 1 "responder rate measured by global pain relief of ≥50% vs baseline at 6 months minimum" was not reported in the CSR." This is factually inaccurate, ≥50% improvement vs baseline in overall trunk and limb pain scores at 6 and 12 months is reported in page 85 of the CSR. Although we appreciate it may be preferable to use the primary composite outcome for the reasons stated by the assessors, the information in the report as it stands is inaccurate. The reason why the results are the same for the primary endpoint and ≥50% improvement vs baseline in overall trunk and limb pain is because the 50% responder rates and composite primary endpoint (with medication component) could be the same if the medication failures were the same as the patients who had <50% pain reduction. As reported in Table 10.2 (page 64) of the CSR, the reasons for primary endpoint failure of <50% overall trunk and limb pain relief at follow-up visit and increase in baseline pain medications within 4 weeks of the follow-up visit were not mutually exclusive.	1	Thank you. We edited the paragraph accordingly.
49	Table 27	Opioid usage should be -3.0 [-22.3, 16.4], p=0.844 (see page 36, Table 17 and CSR page 249)	1	Thank you, we corrected it.

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49	Table 27	"Published safety data from the Evoke RCT study is available for 16 months (mean follow-up time)." This is not factually accurate, although not available in the CSR, 24-month safety data has been published (ref #12 in JCA report) and provided in the HTD dossier.	1	Thank you. The sentence was changed to "Safety data from the Evoke RCT are available up to 16 months (mean follow-up) in the CSR."
53	600-1	"…where the stimulation amplitude is automatically adjusted in real-time to minimise the difference between the measured ECAP." Please add "and the target ECAP" at the end of the sentence otherwise it is not clear what difference is minimised.	1	Thank you, we added the phrase as you suggested.
53	608-10	As mentioned above, PSPS is not a subpopulation of the population that consists of people with chronic intractable pain of the trunk and/or limbs. Both PSPS and a population of people with chronic intractable pain of the trunk and/or limbs are however subpopulations of chronic pain or chronic intractable pain. This is not clear in the JCA report.	1	It was considered that the definition of the full patient population (chronic intractable pain) consisted of not only neuropathic pain. As a result of the PICO consolidation process, PSPS was defined as a subpopulation of chronic intractable pain because PSPS is a type of neuropathic pain.
55	Table 30 All outcomes / Applicability	Same comment as above for page 28 regarding applicability of comparator used.	1	Thank you for your comment. Comments about the applicability are considered outside the scope of the factual accuracy check of the JCA.
56	Table 30 Overall endpoint success /	"The outcome requested in PICO 1 "responder rate measured by global pain relief of ≥50% vs baseline at 6 months minimum" was not reported in the CSR." This is factually inaccurate, ≥50% improvement vs baseline in	1	Thank you. We edited the paragraph accordingly.

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	Applicability	overall trunk and limb pain scores at 6 and 12 months is reported in page 85 of the CSR. Although we appreciate it may be preferable to use the primary composite outcome for the reasons stated by the assessors, the information in the report as it stands is inaccurate. The reason why the results are the same for the primary endpoint and ≥50% improvement vs baseline in overall trunk and limb pain is because the 50% responder rates and composite primary endpoint (with medication component) could be the same if the medication failures were the same as the patients who had <50% pain reduction. As reported in Table 10.2 (page 64) of the CSR, the reasons for primary endpoint failure of <50% overall trunk and limb pain relief at follow-up visit and increase in baseline pain medications within 4 weeks of the follow-up visit were not mutually exclusive.		
58	Table 30	Opioid usage should be -3.0 [-22.3, 16.4], p=0.844 (see page 36, Table 17 and CSR page 249)	1	Thank you, we corrected it.
58	Table 30	"Published safety data from the Evoke RCT study is available for 16 months (mean follow-up time)." This is not factually accurate, although not available in the CSR, 24-month safety data has been published (ref #12 in JCA report) and provided in the HTD dossier.	1	Thank you. The sentence was changed to "Safety data from the Evoke RCT are available up to 16 months (mean follow-up) in the CSR."
59	Table 31	"The planned follow-up of the RCT Evoke study is longer, but the results are not yet published, only up to 16 months	1	Thank you. This sentence was changed to "The planned follow-up for the Evoke RCT was also 24 months but the

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		(mean follow-up time)." This is not factually accurate, although not available in the CSR, 24-month safety data has been published (ref #12 in JCA report) and provided in the HTD dossier.		data were only available up to 16 months (mean follow-up) in the CSR." in tables 28 and 31.
68-9	Table 32	Source not reported.	2	Thank you, we added the source.
69-70	Table 33	Source not reported.	2	Thank you, we added the source.
90	Table 34	Opioid usage should be -3.0 [-22.3, 16.4], p=0.844 (see page 36, Table 17 and CSR page 249)	1	Thank you, we corrected it.
91	Table 34 [C] uncertainty about comparator	Same comment as above for page 28 regarding applicability about the comparator used.	1	Thank you for your comment. Comments about the applicability are considered outside the scope of the factual accuracy check of the JCA.

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