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Committee for Medicinal Products for Human Use (CHMP)

Submission of comments on 'Draft qualification opinion on molecular neuroimaging of the dopamine transporter as biomarker to identify patients with early manifest Parkinsonism in Parkinson's disease' (EMA/765041/2017)

Comments from:

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Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	I found the above referenced document to be clear and compelling aside from one attribute, the title of the qualification opinion. Line 128 of the document is clearer regarding the context of use. I suggest using that language in the heart of the title, such as 'qualification opinion on molecular neuroimaging of the dopamine transporter as an enrichment biomarker for clinical trials in early motor Parkinson's disease'. I think this would enhance the access and use of the opinion	We agree that the title would benefit of modification. Please see title in the final opinion.
2	I would request to use an alternative term for SWEDD also (in addition to SWEDD) for e.g DAT negative as sensitivity and specificity of DAT scan is not 100%.	We prefer that the term SWEDD is used as it is commonly used in the Parkinson's disease literature (e.g Marek et al. 2014, doi:10.1212/WNL.0000000000000424). As it is defined, "subjects with a scan without evidence of dopaminergic deficit", the term does not imply certainty.
3	the title for this document should probably be along the lines of "Qualification of dopamine transporter imaging as a biomarker for Parkinson's disease clinical trials in patients with early Parkinsonian symptoms".	We agree that the title would benefit from modification. Please see title in the final opinion.
4	We recommend that the authors address the diagnostic accuracy of DaT-SPECT for Parkinson's disease as evidenced by imaging-histopathological correlation studies (e.g. Perju-Dumbrava et al., 2012, doi: 10.1002/mds.24000; Walker et al., 2007, doi: 10.1136/jnnp.2006.110122) and longitudinal clinical follow-up studies (e.g. Vlaar et al., 2008, doi: 10.1159/000115640; see also Vlaar et al., 2007, doi: 10.1186/1471-2377-7-27).	In this qualification procedure, diagnostic applications are out of the scope of the proposed context of use for dopamine transporter imaging.

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5	Why is considered only the motor performance as Tremor, Trouble in Moving or Walking, Stooping posture to indicate early stage of PD and not Small Handwriting Loss of Smell, Troublesome Sleeping, Constipation, Low Voice, Masked Face Dizziness or Fainting signs that can often anticipate or accompany the early motor phase. A better definition of early clinical stage PD could be applied for un expert reader.	The criteria for early motor PD used in this qualification procedure are the ones used by the studies included in the analysis data set. In the context of use – enrichment of CT populations, the commented signs and symptoms have not been validated or even commonly discussed by academia and scientific community so far; the analysis plan reviewed and approved by the EMA SAWP was to analyse biomarker performance relevant to progression of motor symptoms as defined by UPDRS Parts II and III. We agree that there are an expanded number of references documenting progression of non-motor features and their role in early PD is still evolving. Finally, EMA SAWP recommended that CPP align with PD UKBB criteria in defining the target population as there is not yet regulatory acceptance of prodromal PD criteria.
6	This document approaches an important issue. The data have been analyzed in an objective manner. I fully agree with this proposal, as it will enrich the population enrolled in PD trials while adding a relatively small cost per patient enrolled. Patient safety will not be affected.	Thank you for your comment.
7	Agreement in general with DATscan as enrichment biomarker	Thank you for your comment.
8	The current title, “Draft qualification opinion on molecular neuroimaging of the dopamine transporter as biomarker to identify patients with early manifest parkinsonism in Parkinson’s disease”, of the referenced document is unnecessarily lengthy and a bit confusing. I would suggest modifying the tile to read “Qualification of dopamine transporter imaging as a biomarker for Parkinson’s disease clinical trials in patients with early parkinsonian symptoms”.	We agree that the title would benefit from modification. Please see title in the final opinion.
9	**Comment:** The inclusion of the data summary section from lines 369 to 518 is helpful and very detailed. However, it seems	The Conrado *et al.* publication is a description of the analyses methods and results to support this qualification procedure. Lines 362 to 500 of the

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	to be more detailed than the general CHMP qualification opinion in lines 605 to 614. Further clarification of the relevance of those details based on the general recommendation would be welcomed. In addition, many of the figures and text are verbatim from the publication by Conrado et al., 2018. It is suggested to remove or at least shorten these sections to the main points and the data originating from these findings should provide a stronger qualification opinion by the CHMP.	qualification document presented selected analyses results and figures which are believed to be valuable to the qualification document. The figures in the publication are key to illustrating the results of the analyses that provided the evidence to support the regulatory qualification decision so we believe including the specific figures is important for the final opinion.
9	**Comment:** Within the background section it may be appropriate to point out some of the potential limitations of the method itself. The in vivo measure is a reflection of Bmax/Kd thus the change in the imaging outcome measure observed especially during a therapeutic intervention may not 100% reflect the changes in dopamine transporter density solely as it also may reflect changes in dopamine itself (see reference further below: Parkinson's Study Group JAMA, 2002).	In this qualification procedure, pharmacodynamic or monitoring biomarker applications are out of the scope of the proposed context of use for dopamine transport imaging. As a reminder, a single baseline measure assessed by visual reads is the intended application and limitations for such use are minimal. Since subjects are being targeted for early in the course of the disease, they will be on minimal medications (i.e. PPMI subjects at baseline are de novo without dopaminergic medications). The PSG 2002 publication referenced is the CALM-PD study which utilized quantitative assessment of scans using β-CIT imaging. It could be added that there is a potential limitation of DAT imaging in that the potential influence of therapeutics resulting in up or down regulation of the dopamine transporter. Yet, this has previously been sought of, and found that there really no data to support this using visual reads, and preclinical studies show that dopaminergic agents appear to have a small if any effect on DAT imaging, this is an unlikely confound in the current proposed context of use.
9	**Comment:** Further clarification why the recommendation is following only a visual read from DATSCAN would be helpful. One of the two studies they utilize for data had both qualitative and quantitative measures but it was not adequately addressed why to exclude a qualitative and quantitative measure of DAT uptake.	As described in the qualification document (lines 744 to 748), PPMI applied visual reads of DAT SPECT scans at baseline using ^{123}I-ioflupane while PRECEPT applied quantitative measures of DAT levels using β-CIT SPECT. The fact that these two studies included in the analysis dataset used different radiotracers and analysis methods led to the confidence that visual

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		reads were sufficient for future use in clinical trials. The use of DAT imaging longitudinally would require quantitative reads. Quantitative reading is not as widely available as qualitative reading, which might restrict the use of DAT as a biomarker. Additionally, the use of visual reads application aligns with the approved use of amyloid tracers for subject selection in AD clinical trials.
9	**Comment:** The document is very long and partly repetitive, often essentially rephrasing methods and results from Conrado et al. (2017). A shorted document, referring to the publication, summarizing key findings, and critically discussing those would be preferred.	The Conrado *et al.* publication is a description of the analyses methods and results to support this qualification procedure. Lines 362 to 500 of the qualification document presented selected analyses results and figures which are believed to be valuable to the qualification document.
9	**Comment:** The document is lacking a comparison to other potential enrichment strategies using combinations of “simple” background and demographic information to identify patients who are more likely to progress on the UPDRS. The added value of a DAT scan and the related procedures could be discussed in this context.	The CPP analysed the predictive accuracy of DAT imaging relative to other parameters (i.e. baseline severity) in the supplementary analyses (lines 501-518). Given that SWEDD status remained an independent and statistically significant predictor of disease progression, this qualification document supports that DAT imaging is a useful enrichment biomarker in early PD clinical trials. This does not imply that DAT imaging is the only viable enrichment strategy, and a combination of enrichment strategies can be explored by sponsors.
9	**Comment:** The classification is based on a visual assessment of the scans. There is only minimal information on the reliability and reproducibility of the results of a visual inspection of the scan. More information would be welcomed.	Reproducibility and reliability of the biomarker is an important consideration. Several published studies have addressed the issue of test-retest reliability of DAT-SPECT imaging. Booij et al. (1998, PMID: 9829575) reported a very low test-retest variability of 7% for FP-CIT. It has been reported that test – retest (i.e., rater/inter-rater) reliability is quite high (Benamer et al., 2000, doi: 10.1002/1531-8257(200005)15:3<503::AID-MDS1013>3.0.CO;2-V) at

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		over 93%. An actual test –retest evaluation of the β-CIT tracer has been performed by Seibyl et al., (1997, PMID: 9293807), the ligand used in the PRECEPT study. In the study of Papathanasiou et al. (2012, doi: 10.1007/s12149-011-0564-1), the degree of interobserver agreement in the visual interpretation of (123)I-FP-CIT images was investigated in 89 subjects blindly evaluated by three separate observers. The authors reported excellent interobserver agreement (κ 0.89-0.93) in classifying studies as "normal" or "abnormal" and fine agreement in assignment of visual scores (κ 0.71-0.80 for putamen and 0.50-0.79 for caudate nuclei). Zaknun et al. (2007, PMID: 17220822) evaluated the effects of different scanners on DAT imaging results and reported that the spatial distribution and image quality of [^{123}I]FP-CIT on different high-resolution systems applying standardized acquisition and reconstruction protocols is less operator dependent and did not affect visual rating of striatal DAT loss. The study of Morton et al. (2005, PMID: 16264363) applied the GE recommended DAT phantom on multiple gamma camera types and compared the relative uptake values. A 5-15% variation between cameras was reported with an intra-operator variation of between 5 and 12% which reflected the proportion of operator intervention within the processing method. There was no statistical variation between operators. The authors concluded that the transfer of a DaTSCAN database between camera types is feasible. The CPP imaging biomarker team is preparing a manuscript that highlights this as well. Such references can be added if EMA deems it appropriate.
10	I suggest to consider to add to the document: 1. Safety data on the recurrent DAT SPECT use, radiation burden on the thyroid and need in its avoidance with the help	A description of the imaging methodology for reliable use of DAT imaging as an enrichment biomarker in PD clinical trials is outlined in the Imaging Methodology section of the Appendix. In addition, lines 214 to 218 of the qualification document mention other sources of information.

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	of Lugol solution. 2. To define minimal permitted time between two scans and maximal number of scans during 2-5 years. 3. To propose the unified protocol for Lugol's solution use (dose, time before scan) 4. To discuss advantages and disadvantages of different assessment ways: visual assessment vs semi/quantitative analysis vs comparison to reference database and to propose the standardised protocols of assessment.	1. Further details on DAT imaging assessment and safety can be also found in the diagnostic device approval documents. 2. As mentioned, DaT SPECT is required to use once only in routine clinical practice for detecting loss of functional dopaminergic neurons in striatum. If there is any issue with the imaging (artefacts) repeat imaging could be done within 06 hours. As a reminder, the current context of use is a single scan at baseline. If an investigator is aware that a patient is frequently participating in CTs should discuss with the patient and the sponsor the benefit of having another DAT assessment. 3. As per EMA recommendations, patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine, for example by oral administration of approximately 120 mg potassium iodide 1 to 4 hours prior to injection of DaTSCAN. 4. The advantages/disadvantages of visual vs quantitative imaging have been described thoroughly in the literature. An independent group, Quantitative Imaging Biomarker Alliance (QIBA) has developed recommendations for quantitative measurements of DAT over time for use to track disease progression or as an efficacy response biomarker for neuroprotection trials. Since the proposed context of use is enrichment and data using visual assessments are deemed adequate, the considerations for quantitative measures would not be needed in this case. Visual assessments are also the method of choice for amyloid radioligands, approved for use for Alzheimer's disease. Noteworthy is that serial measures are not needed for the proposed context

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		of use of dopamine transport imaging in this qualification document. Point #4 is the subject of a manuscript in preparation by the CPP imaging biomarker team.
11	This is an important piece of work that establishes principles that can benefit the conduct of clinical trials. It should help to identify which cohorts of patients are more likely to respond to treatment and establish results that are more unequivocal. However, there are pros and cons to narrowing a Parkinson's sample population in this way. The researchers are able to identify who will progress more rapidly in a narrow sense, excluding non-motor symptoms in particular. The sample is thus more "pure" in one regard, but Parkinson's is very complex and motor symptoms — especially a limited set — are only part of the picture at any point in disease progression. While the researchers no doubt know this, the frustration with a slow discovery of a reliable biomarker for Parkinson's is that this naturally encourages ways to exclude patients who "clutter" findings. The challenge here is that while the use of DAT deficiency plus limited clinical indicators as described in the draft provides a non-cluttered sample population, the disease is by nature cluttered. The researchers risk studying one piece of the jigsaw, so to speak, and then making generalizations to the jigsaw as a whole. In this sense, the procedure outlined is a step back to the time, not so long ago, when researchers ignored non-motor symptoms of Parkinson's which are often more concerning to patients.	This qualification document supports that DAT imaging is a useful enrichment biomarker in early PD clinical trials. This does not imply that the use of DAT imaging is mandatory or is the only viable enrichment strategy (line 614). DAT imaging-based enrichment should be used in a trial-specific manner, depending on the therapeutic candidate being evaluated, the type of trial design being considered, and the intended population being targeted. This allows sponsors to make the decision to enrich, versus not enrich. The views expressed in this comment are clearly a reflection on the changes emerging on how PD is viewed. The CPP team clearly has focused on a single biomarker as a tool for enrichment in clinical trials based on data to date. Evaluation of SWEDD incidence in clinical trials has been reported in several distinct clinical trials beyond those that were analysed in this opinion. Risk / benefit of implementation of DAT at baseline for subject selection in trials aligns with FDA's draft guidance from 2012 (Enrichment Strategies for Clinical Trials; https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm332181.pdf). Regarding the comment "slowness of symptom onset does not mean Parkinson's is absent." Note that the context of use is not diagnostic accuracy and the exclusion of subjects less likely to progress has impact to trial design and sample size. Clearly more data is needed to identify other factors that contribute to disease progression and this is the current focus of CPP.

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	So, while the research should proceed, it should be done with considerable recognition that Parkinson's patients vary widely in the types of symptoms they exhibit during the course of the disease and that slowness of symptom onset does not mean Parkinson's is absent. Generalizations from studies relying on this procedure should therefore be limited. Consideration should be given to how volunteers for the trial that are rejected for inclusion are be managed and their likely disappointment handled.	
12	The principle of improving enrichment of clinical trials targeting disease modification is understandable and should be pursued. However, there are numerous problems with the initial qualification document that have affected the final CHMP Qualification opinion. In particular DAT SPECT cannot be considered a valuable instrument to identify PD patients who are more likely to progress since there is no relationship between baseline striatal uptake and disease progression. It could be considered as screening tool for early identification of misdiagnosed Parkinson patients (SWEDD) for research purposes. However, this is not in line with its current clinical indication. The FDA indication for DatScan quotes: "DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other	As described in lines 584 through 586, DAT imaging status herein was found to be a statistically significant predictor of disease progression, as measured by the MDS-UPDRS Part III scores. In this qualification procedure, diagnostic applications are out of the scope of the proposed context of use for dopamine transport imaging. The regulatory documents cited in the comment relate to the approval of DAT imaging as a diagnostic device; in addition, the document contents are based on the state of the scientific evidence at that time. This document is not aimed at qualification for application of the biomarker in daily clinical practice, as this is covered by the approved FDA and EMA indications. This document covers the proposed application of DAT imaging limited to the drug development setting. Note that DaTScan has been implemented in larger screening type of studies to identify those subjects at risk for development of PD (Jennings et al., 2017, doi:10.1001/jamaneurol.2017.0985). Widespread use and approval of neuroimaging tracers is gaining greater acceptance for multiple CNS diseases as a way to enable early intervention which holds the most promise to slow disease progression.

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	diagnostic evaluations “ The EMA indication for Datscan use is: “DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum: In adult patients with clinically uncertain Parkinsonian Syndromes, for example those with early symptoms, in order to help differentiate Essential Tremor from Parkinsonian Syndromes related to idiopathic Parkinson’s Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. DaTSCAN is unable to discriminate between Parkinson's Disease, Multiple System Atrophy and Progressive Supranuclear Palsy. In adult patients, to help differentiate probable dementia with Lewy bodies from Alzheimer’s disease. Indeed, the presence of abnormal striatal DAT binding does permit diagnosis of PD. On the other hand, performing DatScan as screening tool would expose more than 85% of enrolled patients to unnecessary radioactive tracer injection and procedure. Use of central visual reading is viewed as critical and operator independent methods of analysis should be implemented. In conclusion, it is suggested that DatScan imaging is considered an optional investigation to be performed in conjunction with structural imaging in patients with reasonable uncertain clinical diagnosis and according to current product labelling.	It must be highlighted that “enrichment tool” does not mean “screening tool”; for enrichment, patients are usually invited to perform enrichment exams, but are usually not compulsory for participation. Qualitative vs quantitative reading has been discussed. Qualitative reading has been shown to be appropriate for qualifying DAT for enrichment and has the advantage of being available at most study centres, accounting for generalisability of the tool.

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13	The qualification of molecular imaging with DAT as an enrichment biomarker has the potential to have important impact in design of clinical trials in early manifest PD, in excluding those subjects (SWEDDs) who are likely to progress slowly and are likely not to have the underlying pathology that is being targeted by an experimental treatment. Biomarker qualification has the potential to accelerate update of this biomarker by clinical trial Sponsors, compared to current use of biomarkers on a protocol-specific basis.	Thank you for your comment.

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
	2	Comment: The proposal only involved visual assessment of DaT scan. There are reports in literature suggesting that structural defects like infarct or tumor around basal ganglia interfered with the interpretation of DaT scan though the incidences are rare (Parkinsonism Relat Disord. 2010 Jun;16(5):356-7.). Moreover, there are reports of DaT scan being equivocal though very rare. This issue is important in relation to point 7 of **Intended Application.** Proposed change Please dedicate few lines to cover above points with reference if possible. This won't affect the study design or protocol.	The examples highlighted by this reviewer relate to use of DAT imaging in clinical practice. In a clinical trial setting, other evaluations performed as entry criteria are implemented to exclude the possibility of enrolling subjects with tumors or infarcts (Figure A1: lines 728-732). As stated by the commentator, this won't affect the study design or protocol, and the qualification procedure was not centred on demonstrating the accuracy of DAT imaging to detect true dopamine deficiency, but rather it's utility as an enrichment biomarker, given its current use and imaging interpretation, with all the potential variations that it carries.
	2	Comment: The draft should have one line mentioning that DaT scan can have visual, semi-quantitative and quantitative assessment methods. Proposed change (if any): Include one line	Such information has been provided in lines 1022 and 1023. We can also include this information in the main body of the document if EMA deems it appropriate.

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Line 728	2	Comment: In the section **Background on the biomarker** It should be mentioned that at least 50-70% Dopamine receptor degeneration is needed before clinical symptoms become obvious (Marsden CD. Parkinson's disease. Lancet. 1990;335: 948–52. Lang AE, Lozano AM. Parkinson's disease. First of two parts. N Engl J Med. 1998;339:1044–53.) Proposed change (if any): Please add lines to include the information if possible.	Amended accordingly.
Line 262	4	Comment: Typo in the reference number Proposed change (if any): The transformation of the individual UPDRS Part III subtotal score to the respective MDS-UPDRS relied on a previously derived formula based on a Hoehn and Yahr stage I or II (~~7~~***1***6)	Amended accordingly.
Line 288-293	4	Comment: The study aims to describe the CID but the text gives importance	Amended accordingly.

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		only to the minimal CID. Consistent terminology should be used in the text. Proposed change (if any):	
Line 292	4	Comment: Multiple UPDRS part III meaningful change estimates exist. An explanation for use of the Shulman MCID could be provided. Proposed change (if any):	Amended accordingly.
Page 5/35, lines 157-158	7	Comment:The UK Brain bank criteria always require bradykinesia (+ tremor or rigidity). The “tandem” rigidity/tremor (see also page 4, line 134-135) should therefore be excluded in the target population. Alternative: The UK Brain Bank criteria are **not** used Proposed change (if any):	Thank you for sending this clarification. If EMA deems appropriate the document can be revised to assure accuracy of the description of the UKBB Criteria as follows: Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions). And at least one of the following: a. muscular rigidity b. 4–6 Hz rest tremor c. postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction. The EMA recommended in a 2015 SAWP meeting that the context of use adhere to the UKBB criteria.
Page 6/35, line 207	7	Comment: Why only qualitative evaluation. In “borderline cases” a n additional quantitative evaluation could	As described in the qualification document (lines 744 to 748), PPMI applied visual reads of DAT SPECT scans using 123I-ioflupane while PRECEPT applied quantitative measures of DAT levels using β-CIT

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		be helpful Should the evaluation always be done by the same examiner? Will he/she be blinded? Proposed change (if any):	SPECT. The fact that these two studies included in the analysis dataset used different techniques led to the use of visual assessments as opposed to (semi-) quantitative assessments. Information on imaging methods including training of readers can be found in the Appendix (line 818 and forward). A manuscript on the methodology recommendations is currently being prepared by the CPP biomarker team. At present there is some interest in applying semiquantitative assessments for borderline cases in observational/research studies. The current context of use is for trial enrichment so having a few subjects that may be SWEDD enrolled vs excluded from the study has limited risk overall.
115-125	9	**Comment:** The text here is slightly redundant with information provided earlier in the document in the executive summary and background sections. It may be good to review the text and slightly modify redundant information and precise the messaging.	Amended accordingly.
277ff	9	**Comment:** There is a need to clarify why the baseline score was not included in the primary model	While the primary and supplementary analyses indicate that the DAT imaging status is a statistically significant predictor of the disease progression rate, the supplementary analysis shows that the association between DAT imaging status and progression rate remains statistically significant (two-tailed P-value < 0.01), even after the effect of baseline on progression rate has been accounted for.
294-295	9	**Comment**: The investigation of the appropriateness of the linearity	Analyses included progression over both 24 and 41 months in duration for evaluation of the biomarker performance on clinically meaningful

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		assumption over the range of 41 months needs more attention, in particular since the reference article by Conrado mainly deals with a 24 months period.	change. The context of use applies to clinical trials for up to 2 years in duration yet predictability over longer time points is also very relevant to assure confidence in the predictive accuracy over time. A more comprehensive, longer-term non-linear mixed effects model is under development. As per EMA feedback, and given the analysed data in this qualification procedure, changes in the MDS-UPDRS Part III are adequately captured by a linear model.
307	9	**Comment**: Clarification is welcomed on why the 90% confidence intervals are presented rather than the conventional 95% two-sided confidence interval.	As presented in lines 270 through 275, the research hypotheses were tested at one-tailed alpha of 0.05. in such a case, a 90% CI facilitates the readers interpretation.
387ff	9	**Comment**: The impact of missing values due to dropouts on the interpretation of the results needs more attention. The statistical models using a missing at random assumption which may not be appropriate or at least needs more discussion and sensitivity analyses applying different dropout mechanisms are required. The role of baseline characteristics on missing value patterns are described in the reference article, but not the role of the missing values on the interpretation of the results.	A dropout model was developed to help elucidate the missing data mechanism (please refer to Conrado et al., 2018, doi: 10.1111/cts.12492). A Gompertz distribution could describe the dropout pattern in both studies included in the dataset (Conrado et al.; Figure 1). This is evidence against a 'missing not at random mechanism', and evidence in favour that the developed disease progression model did not suffer of bias due to the missing MDS-UPDRS Part III scores.
613-614	9	**Comment:** 'does not mandate the use of DAT' **Proposed change (if any):** Our current understanding of the document	EMA's guideline on the qualification of novel methodologies in drug development, which governed the regulatory review of this procedure, clearly states that qualification opinions do not constitute mandates for use of the tool by industry sponsors.

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		is the provision of feedback on the use of imaging, therefore a stronger recommendation than 'does not mandate' would be useful to help guide industry in the use and further development of molecular imaging in patients with PD.	
731 Figure A1	9	**Comment:** This is a helpful figure, however it would be easier to read if it could be slightly modified to signify that each of the four potential inclusion criteria are met or if the boxes represent steps which need to be followed from top to bottom. Maybe a slight modification of the figure or further explanation in the figure legend would further clarify. From our current understanding of the figure, one needs to follow the steps for inclusion criteria with the last one being an imaging outcome measure.	Amended accordingly.
828-829	10	Comment: It is mentioned that "an iodine allergy is not a contraindication to receiving this tracer" However, iodine allergy is a known contraindication to the Lugol's solution use, which is used to avoid radiation burden on the thyroid. Proposed change (if any): to consider to add iodine allergy to the	The general subject of "iodine allergy" is open for discussion, as iodine/iodide is essential for normal health, which requires a daily dietary intake of iodine of 250-600 µg/day - for T3 and T4 thyroid hormone biosynthesis[1] 1. Harbert JC, Gonçalves Rocha AF: Textbook of Nuclear Medicine. 2nd ed. Philadelphia: Lea & Febiger, 1984: 4. Please consider following facts:

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		contraindications. Ove	1. The 185 MB dose of DaTSCAN contains approx. 4ng of free iodide (I-), which is much less than the daily dietary intake, or the 15g injected as CM for an enhanced CT. 2. The molecule of Iodine and iodinated compounds could act as an allergen but iodide (the negative ion of iodine) does not produce allergy reactions. 3. The incidence of severe side effects after single doses of iodine was well established after the Chernobyl experience where millions of subjects were treated with Iodide at much higher doses. The incidence of severe adverse reactions was 1 case per 10 million in children and 1 case per million in adults. In those documented iodine allergy patients (probably allergic to some iodine compounds like topical antiseptics or seafood allergy) where early and accurate diagnosis of nigrostriatal degeneration could be relevant, scans with DaTSCAN could be performed. In case of going ahead, there are some recommendations to follow: 1. Do not block thyroid gland with Lugol solution because the high Iodine concentration (approx. 5 g/ 100 ml). The alternative is using perchlorate or not blocking the thyroid. 2. Premedication with corticosteroids and/or H1/H2-antagonists may protect against some symptoms of possible hypersensitivity reactions. Although it is very unlikely because

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			I123 is not released.
Lines 49-51	12	Comment: There is no evidence that identification of reduced DAT binging can effectively predict clinical progression in PD patients. Recent neuropathology evidence has suggested that there is no relationship between striatal DAT binding and number of nigral dopamine cells. Considering the uncertain mechanisms associated with neurodegeneration and in light of past experience with DAT SPECT in clinical studies (i.e. CALM-PD) the possibility that any candidate drug would interact with DAT membrane expression or binding cannot be excluded, which would affect study outcome. However, this would not apply to the condition of DatScan performed before experimental therapy initiation where SPECT is used exclusively for trial enrichment. Proposed change (if any): OMIT THAT STATEMENT	A discussion on the potential for certain concomitant medications to interfere with binding of 123-Ioflupane is provided in lines 837 through 864. The comments here would be applicable to the use of DAT as a biomarker of disease progression yet do not apply for its use for subject selection in a trial. Candidate drugs will not yet be onboard to patients being enrolled in a trial. And in many cases, they will be de novo patients without any treatments yet.

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Line 88	12	Comment: The above statement is based on the results of only 3 studies where patients with different diagnosis were included (Karimi M, Tian L, Brown CA, et al. Validation of nigrostriatal positron emission tomography measures: critical limits. Ann Neurol 2013;73:390–396) Recent evidence has questioned the existence of such correlation both in PD (Saari L, Kivinen K, Gardberg M, Joutsa J, Noponen T, Kaasinen V. Dopamine transporter imaging does not predict the number of nigral neurons in Parkinson disease. Neurology. 2017 Apr 11;88(15):1461-1467) as well in other PD-like synucleopthies i.e. Dementia with Lewy body. A recent study suggested that among patients with DLB coming to autopsy, 10% met pathologic criteria for Lewy body disease (including nigral dopamine neurons deposition) but had normal 123I-FP-CIT imaging (Thomas Ai, Neurology 2017) Proposed change (if any): OMIT THAT STATEMENT	Numerous publications in nonclinical models demonstrate the correlation between DAT terminal loss and functional DAT imaging with nigral neuron degeneration. The studies referenced by this reviewer are human post-mortem data. These findings show that reductions of DAT radiotracer binding occur in conditions with substantial loss of presynaptic nigrostriatal neurons. The study by Saari published last year in Neurology has significant limitations in that they only performed TH+ve cell counts in a few sections from the SNpc, and whilst they did use stereology they should have counted cells on staggered sections all the way through the SNpc in order to get an accurate assessment of the total number of TH+ve neurons. Hence, they do not know the total number of TH+ve neurons, thus their correlations are not valid, particularly since they are assessing the DAT binding in the whole striatum. It is known that there is a regional loss of dopaminergic neurons in the SNpc so although they say the samples were taken around the third nerve root the extent of the cell loss in that region will vary markedly between subjects. Additionally, they are also not comparing “like with like” i.e. they are comparing immunohistochemistry derived physical cell counts with the DAT binding potential which is very problematic. Also the loss of terminals occurs before cell bodies, so the two counts don’t match. That said for the EMA qualification, even if the Saari publication was correct, it wouldn’t matter since there is a differential in the DAT binding and hence loss of terminals, which can be picked up in visual reads, so as to distinguish between controls/SWEEDs and Parkinson’s and Parkinson’s related disorders. For Parkinson’s there is asymmetrical loss of DAT but you can still see the tails of the putamen. Additionally, since the terminals of the nigrostriatal pathway are the functional part of the system they equate more with motor symptoms/responses to drugs and hence whether the DAT binding correlates or not with the number of cell bodies in the SNpc is not important.

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			Most important for this topic is to note that the context of use for this application is for subject selection in clinical trials for the purposes of enrichment of subjects more likely to progress yet not for the purposes of neuronal degeneration or monitoring treatment response. As a reminder, the target population is early motor PD rather than late stage PD.
ROW 100	12	Comment: 123I-ioflupane is approved in Europe for the differential diagnosis between essential tremor and other parkinsonian disorders but NOT for the differential diagnosis of Parkinson's disease. This aspect is very important because identification of reduced DAT binging is NOT specific of PD and it can be observed in many other degenerative parkinsonisms as well as in presence of vascular lesions of the basal ganglia. Assessing in an elderly population brain 123I-ioflupane uptake without structural imaging does not permit to distinguish patients with PD from those with vascular parkinsonism since both would present with reduced striatal binding. (Antonini a et al. The relationship between cerebral vascular disease and	The current application in this Qualification Opinion is not diagnosis or differential diagnosis. Enrichment applications do not require diagnostic accuracy and it is acceptable to use DAT in our own applications to exclude those less likely to progress (even despite the biomarker not being specific for PD)

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		parkinsonism: The VADO study. Parkinsonism Relat Disord. 2012 Jul;18(6):775-80) Proposed change (if any): CHANGE TEXT ACCORDINGLY	
Row 178-179	12	Comment: As for the above comments presence of abnormal DAT imaging does not equal diagnosis of PD and does not exclude the possibility of wrongly exposing non-PD individuals to any experimental drug. By contrast, the ethical aspects of unnecessary exposure of large patient groups to a radioactive tracer to for confirmatory purposes should be considered. This is also in contradiction with the statement that the use of DAT imaging for diagnostic applications was out-of-scope for this document (row 183). Proposed change: REVISE	EMA proposes to revise the wording in line 178-179 from “The use of DAT imaging would allow the exclusion of subjects unlikely to have the diagnosis of PD….” to “The use of DAT imaging would allow for enrichment of a patient population with a DAT deficit to more effectively evaluate an intervention in a clinical trial.” The availability of a disease modifying therapy for PD is a major unmet need. The potential for the development of an intervention that improves the lives of individuals with PD offsets the risk for radiation exposure for eligibility testing in clinical trial participants. This is especially important as the field moves to early intervention in PD, there is a lack of available tools and actionable screening approaches to accurately select subjects for clinical trials beyond clinical criteria alone. Many trials in other CNS diseases have found that a significant proportion of the subjects lacked the target or neuropathology (e.g. Amyloid) when it was too late. The risk of not employing DAT imaging is that many trials could fail by not enrolling the appropriate subjects and wrongly exposing subjects unlikely to progress to therapeutic candidates. In the area of Alzheimer’s disease PET imaging is being employed in large screening studies to recruit subjects for primary and secondary prevention.

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Row 193-194	12	Comment The indication of single site reading is particularly critical and raises ethical and technical issues. Monopolizing reading to one institution introduces a significant bias as one specific institution will receive a financial incentive to promote the use of the biomarker. There is no evidence that central reading is more effective that reading at multiple institutions with consensus in case of disagreement. Indeed, the PPMI study all participating subjects were aligned in terms of their imaging acquisition protocol including the time interval between injection and SPECT reading. Proposed change: Revise to consider decentralized reading or operator-independent analysis	GCP guidelines have shown the value of centralization of imaging reads for clinical trials. This does not mean that DAT imaging interpretation for individual patient care should be centralized, but that imaging interpretation for clinical trials should be centralized, to whatever properly accredited lab that has the capacity to do the job.
Row 204	12	Comment: This is not true in Europe where 18F-Fluorodopa is also registered for clinical use and commercially distributed Proposed change: Add 18F-Fluorodopa	Amended accordingly.
Row 326 Row 377	12	Comment: The number of SWEDD has been reported lower in other datasets and an estimate of 10% would be more realistic. A power calculation with an estimate number of so called SWEDD	The context of use for this application is based on a particular target population. We agree that for patients that are further along in the course of the disease, such use would not be needed. The simulation results presented in the qualification package are intended to be illustrative examples and are based on specific assumptions (and

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		below 10% would yield to very different conclusions regarding the need to include a mandatory DAT SPECT confirmation for clinical trial enrichment. Proposed change: Integrate power calculation	defined stage of the disease). Sponsors can vary the assumptions depending on the intended target population, the type of drug being evaluated and the type of clinical trial design being considered.
Row 522	12	Comment: The authors in the document report 13% which is <15% and in row 525 they indicate a range between 3 and 15% in the literature	In line 522, the sentence should read: “The rate of SWEDD subjects in the PPMI observational cohort is **approximately** 15%”. This sentence will be corrected.
Row 728-729	12	Comment: The proposed diagram assumes that: 1) it is possible to exclude patients with atypical parkinsonism clinically, which is not correct as neuropathology studies have consistently demonstrated. These individuals will still be enrolled because DAT SPECT will show reduced binding 2) Presence of abnormal DAT binding does not exclude patients with vascular lesions in the basal ganglia and this would require additional structural imaging confirmation of absence of striatal signal abnormalities by MRI or CT. 3) Introducing mandatory DAT SPECT means exposing more than 85% of the	As described in lines 584 through 586, DAT imaging status herein was found to be a statistically significant predictor of disease progression, as measured by the MDS-UPDRS Part III scores. In this qualification procedure, diagnostic applications are out of the scope of the proposed context of use for dopamine transport imaging. Moreover, as stated in lines 613- 614, the use of DAT imaging is not mandatory.

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		enrolled patients to unnecessary injection of a radioactive tracers. Patients who cannot perform DAT SPECT would be excluded from such studies even if they fulfil completely PD diagnostic criteria. 4) Baseline Dat Scan uptake does not predict rate of progression. Therefore even by using such evaluation PD with slow or no progression would still be included. The current diagram erroneously assumes that all PD patients with reduced DatScan show significant progression.	
4-7	13	Comment: I feel this title might suggest that DAT imaging is a “diagnostic test” for Parksons disease. The rest of the qualification opinion emphasasises the use of the biomarker for enrichment, and in particular to exclude those subjects who are likely to progress slowly. Proposed change (if any): Draft qualification opinion on molecular neuroimaging of the dopamine transporter an enrichment biomarker to	EMA agrees that the title would benefit of modification. Please see title in the final opinion.

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		select patients for clinical trials in early manifest Parkinson’s disease	

Please add more rows if needed.