European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

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OVERVIEW OF COMMENTS RECEIVED ON DRAFT GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF PARKINSON'S DISEASE

Table 1: Organisations that commented on the draft Guideline as released for consultation

	Name of Organisation or individual	Country
1	Biogen Idec and Vernalis	
2	BRANE DISCOVERY H.	
3	EFPIA	
4	H. Lundbeck A/S	
5	PSI Regulatory Subcommittee	
6	Schering –Plough	
7	Dementias & Neurodegenerative Diseases Research Network (DeNDRoN)	

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Table 2: Discussion of comments

GENERAL COMMENTS - OVERVIEW
BRANE DISCOVERY H. We have noticed that the Guideline refers only to "de-novo" patients or patients treated with L-dopa, while therapy with dopamine agonists (DA-agos) either alone or in add-on have not been included *Reply: Here is dealt with in the document e.g. section 4.3 Polytherapy, section 6.2 Study design and within the text at several points.*
EFPIA Overall, this draft guideline is comprehensive in scope, and the coverage of disease modification and Parkinson's Disease Dementia is welcome. The following statement in line 63 of the Introduction is considered to be pivotal to the development of medicinal products for the treatment of Parkinson's Disease (PD): "In general, a patient with early stage PD will start with dopamine-agonists." This statement accurately reflects L-Dopa sparing strategies used in current clinical practice with the intention of limiting the occurrence and severity of motor fluctuations. This clinical practice is expected to shape the way in which the PD population is expected to develop over the coming years, however this does not appear to be reflected in the remainder of this draft guidance document. It is anticipated that as more patients with early stage PD are prescribed dopamine-agonists, the patient population receiving L-Dopa as monotherapy will decrease in size and therefore it is considered necessary to identify alternative populations, for example patients currently receiving L-Dopa and dopamine-agonists, in which to investigate symptomatic relief. *Reply: No comments.* In addition, there are some key points requiring discussion and clarity, to enable the provision of clear and clinically viable guidance on the development of treatment for Parkinson's Disease: • The unsuitability of the use of a placebo-control in long-term studies in patients with early-stage PD. • The similarity of the two groups, "Patients on L-Dopa with insufficient control of motor symptoms", and "Patients on L-Dopa with motor fluctuations". • The desirability of a reduction in L-Dopa treatment during the course of treatment. • The need for titration of doses for individual patients according to response. • Some confirmation on the current validation position for biological markers of PD • Some guidance on the value of 'delayed start' study designs as a method of demonstrating disease modifying rather than symptomatic effect • Further clarity on the design for disease modification studies in de novo patients *Reply: Placebo-controlled studies in Parkinson's diseases are deemed necessary given the variability in signs and symptoms. The other issues are dealt with in the comments throughout the text.* Finally, although there is an extensive reference list on pages 12 to 14, there are areas where it would be helpful to cite the reference used in support of specific statements. This applies throughout the guideline, but examples include Page 3, Section 1, Lines 31-32 (clinical/operational diagnosis of PD), and Page 4, Section 1, Lines 54-55 (epidemiological statistics). *Reply: No comment.*

PSI

Some ICH E9 topics are arbitrarily selected for discussion in the text without any clear reason why they would add value to this guideline. In most cases it is sufficient simply to reference ICH E9 (or other statistically related guidelines such as ICH E10 and the series of CHMP statistics guidelines) to reduce the guideline text and to reduce the chances of between guideline inconsistencies. We suggest that only text that deliberately amplifies (or explicitly over-rules) ICH E9, or other statistically related guidelines, is included in this therapeutic guideline.

Reply: Taken into account. See comment further on.

SCHERING-PLOUGH

Parkinsonism is a common movement disorder syndrome. Parkinson's disease (PD) is the most common cause of Parkinsonism and the second most common neurodegenerative disease. The central feature of Parkinson's Disease is a disruption of dopaminergic neurotransmission in the basal ganglia with a progressive loss of dopaminergic neurons in the substantia nigra and appearance of Lewy bodies and Lewy neurites in many areas of the brain. Although motor abnormalities predominate and, usually initiate the clinical problems, other clinical features such as change in cognition, autonomic abnormalities, and sleep disturbances contribute to the decline in quality of life. The motor symptoms themselves, bradykinesia, tremor, rigidity, and postural instability, appear in varied sequence and severity. Although the cause of the sporadic disease is unknown, there are documented viral and toxic etiologies as well as genetic contributions of varying significance. Diagnosis depends largely upon the clinical features and exclusion of secondary Parkinsonism; however, recent studies investigating imaging and biochemical biomarkers suggest potential diagnostic and theranostic roles for C 11 raclopride PET, F 18 dopa PET, and FDG-PET as well as mitochondrial complex 1 measurements, α-synuclein levels and isoforms in blood, and genetic screening. The role of these new tools should be considered when drafting the final guideline.

There is no therapy that is as yet shown to alter the course of the disease. Due to the variable and progressive course of the disease, symptomatic therapies require recurrent adjustments in dosage or combination of therapy. Most therapies are currently directed at motor symptoms but symptomatic treatment of the cognitive, psychotic, sleep and autonomic features are often required and recognition of these features is lacking in this draft guidance.

The most successful anti-Parkinson agent today is levodopa (combined with a peripheral decarboxylase inhibitor) although, because of the limiting side effects of L-dopa, other agents such as direct dopamine agonists and COMT inhibitors are frequently used early in the course of the disease. Treatment limiting side effects of L-dopa therapy include on-off phenomena, peak drug effect dyskinesias, and hallucinations. Any new agent should be considered in light of their ability to avoid such complications.

Reply: Taken into account.

DeNDRoN

There is nothing about the importance of PD subtyping as part of clinical trial design (e.g. tremor dominant and axial forms).

Reply: The subtyping referred is at discussion. The current status is that it usefulness needs to be established. An MAH is however is free to study these subtypes separately or within one study.

Does EMEA have advice on how to proceed further in trials where selected individuals have responded exceptionally well but overall the results are negative?

Reply: This broad question can only be answered in general terms. If the overall results are negative this will, in general, imply an inconclusive study. If in a selected group of individuals an exceptional response is observed and some prognostic factors can be identified this is considered hypothesis generating. An additional confirmative study is then required.

SPECIFIC COMMENTS ON TEXT

EXECUTIVE SUMMARY

Line no.[1] + paragraph no.	Comment and Rationale	Outcome
Biogen Idec and Vernalis- Line 13-15 lines 243-245	See discussion line 234-245	See discussion line 234-245

1 INTRODUCTION

Line no. + para no.	Comment and Rationale	Outcome
EFPIA - line 18 "…. degeneration of heterogeneous populations of neural cells **(especially dopaminergic neurons) "**	To be coherent with Line 57 where "dopaminergic cell loss" is mentioned, it is suggested to revise the wording by adding "especially dopaminergic neurons".	Agreed an although a different wording is proposed: "…. degeneration of heterogeneous populations of neural cells **(e.g. dopaminergic neurons) "**
PSI- lines 26-30	It would be helpful to quote the same "age ranges" for incidence and prevalence to enable this information to be used effectively.	Based on the literature where these cut-off points were presented. Major message is that incidences and prevalence increases with age. **No changes are deemed necessary.**
EFPIA - line 31 "The clinical diagnosis of PD required bradykinesia and at	On line 36, "4 core symptoms" are mentioned but not listed while they are listed in line 31. Thus, it is suggested to revise the sentence by adding "core	**Agreed and adapted accordingly.**

[1] Where applicable

least one of the following resting tremor, muscular rigidity and postural reflex impairment **(core symptoms)**."	symptoms" to make it clear what are these 4 symptoms	
DeNDRoN page 3 lines 48/9).	Parkinson's Disease Dementia (PDD) is strictly related to Dementia with Lewy bodies (DLB) but may overlap considerably with Alzheimer's Disease." is unclear.	This is clarified in the next sentence referring to the co-existence of amyloid plaques and Lewy bodies
EFPIA - line 37-76 Magnetic Resonance Imaging (MRI), Monoamine oxidase (MAO), Cathecholamine-O-methyltransferase (COMT)	Spelling of acronyms would be welcome.	Agreed. Adapted accordingly.
EFPIA - line 43 "Other signs and symptoms that may be present or develop during the progression of the disease are postural reflex impairment, autonomic disturbances (sialorrhoea, seborrhoea, constipation, micturation disturbances, sexual functioning, orthostatic hypotension, hyperhydrosis), sleep disturbances, ~~and~~ disturbances in the sense of smell or sense of temperature **and pain**	As many PD patients complain of pain symptoms it is suggested to add this to the list.	It is acknowledged that many Parkinson patients complain of pain. However, pain is considered neither specific nor pathognomic for Parkinson's diseases. **No changes are deemed necessary.**
DeNDRoN	The statement that dopamine agonists are the usual first treatment for PD is incorrect and there is no evidence to support this (see NICE guidelines).	In the paragraph before it is stated that patients with early stages of PD may start, **depending on the clinical context,** with a dopamine-agonist or a dopamine precursor (L-Dopa+). It is acknowledged that across Europe there is no uniform proposal on initiating symptomatic medication for PD. In general however younger patients who form the largest proportion will start with dopamine-agonist and elderly patients

		with L-dopa.
2. SCOPE		
Line no. + para no.	**Comment and Rationale**	**Outcome**
EFPIA - line 83	There are some typos, or missing words that would need revision.	"The scope **<u>of</u>** ~~is~~ this document" is corrected.
4. SPECIFIC CONSIDERATIONS		
Line no. + para no.	**Comment and Rationale**	**Outcome**
4.1 Design of the clinical studies		
Biogen Idec and Vernalis General comment	**Three arm trials in both Early and Late PD** Whilst it is recognized that a three-arm placebo/active controlled double blind study is a perfect design, there is often wide geographical variability of the first choice active treatment for early PD or indeed as additional to L-dopa in more severe disease. Some geographies prefer L-dopa whilst others prefer dopamine agonists. In addition even within dopamine agonists different geographies have preferences (bromocriptine, lisuride etc). This makes multinational trials difficult. There should be an alternative approach of a placebo-controlled trial and a separate active controlled trial to allow for choice as to which approach companies find most practical. **Superiority/ non-inferiority trial designs** Active comparator trials mention superiority. Given the difficulty of proving superiority and sometimes difficulty in performing placebo controlled trials, the guidance should allow non-inferiority designs for efficacy if certain safety aspects of a new drug are expected to be seen. In this case safety en-points (e.g. postural hypotension) could be superiority end-points.	The Neupro case (see EPAR Neupro) confirms the necessity and feasibility of the study design required. Head to head 3 arms studies with placebo and active control are needed. **No changes are deemed necessary.**

Biogen Idec and Vernalis Lines 105-122 Under the Line 110 add to the second sentence: The following study objectives can be distinguished, **however it is recognised that some of the objectives may overlap in PD population. Therefore these objectives are just a guide and there may be other objectives established, depending on the mechanism of action of an investigational product and suitable target patient population.**	4.1 Design of the clinical studies – division of patients in different subgroups depending on L-Dopa therapy and severity of motor fluctuations. **Comment:** It is hard to make a clear-cut definition of subgroups of PD patients based on the criteria of L-Dopa usage and severity of motor fluctuations. The boundaries between patient subgroups are somehow artificial and an overlap in manifestation, especially of motor symptoms, can be easily seen in clinical practice.	Agreed and in accordance to lines 149-174 dealing with motor fluctuations although a different position and wording is proposed: "The following study objectives can be distinguished: - - - …. ***"It is acknowledged that some of the objectives may overlap in PD population. These objectives are a guide and there may be other objectives that can be justified."***
DeNDRoN The categories under 4.1 are not logical, with significant overlap between subheadings.	The categories under 4.1 are not logical, with significant overlap between subheadings.	See answer above
Brane Discovery S.r.l. Lines 105 We suggest to include study designs for symptomatic relief in patients with early- or mid-stage Parkinson's Disease receiving one or more DA-agos.	In the last 5-10 years DA-ago therapies have been commonly used worldwide in early- or mid-stage P.D. patients. The rationale was to delay as far as possible the start of the L-dopa therapy and consequently the possibility of developing L-dopa related dyskinesias. In this paragraph (4.1 page 5) treatment with DA-ago has not been considered.	This is covered in the by the section Symptomatic relief in early-stage PD before L-Dopa+ treatment. Dopa-agonists are not specific mentioned as other agents could be used as well (anticholinergics, combination therapy). Head to head 3 arms studies with placebo and active control are needed. **No changes are deemed necessary.**
EFPIA - line 117 "Therapies aimed to modify disease progression, **or to postpone** late motor complications"	There are some typos, or missing words that would need revision.	There is no typo, it is worked out in the subsequent paragraphs.

EFPIA - line 127	Does "*de novo*" means no concomitant L-Dopa or no treatment at all? Please clarify	De novo here in principle means no concomitant L-dopa. **Adapted accordingly**
EFPIA - line 131 "Thus incorporation of a placebo-arm allows the distinction between a genuine treatment effect and **variations in** ~~spontaneous~~ motor **symptoms** ~~fluctuations~~ in early-stage PD"	The statement *'Thus incorporation of a placebo-arm allows the distinction between a genuine treatment effect and spontaneous motor fluctuations in early-stage PD'* could lead to confusion. The latter part of the sentence could be associated to late Dopa-related motor fluctuations.	Agreed. **Adapted accordingly.**
EFPIA - line 132 ~~Given the slowly progressive course and mild stage of the disease a placebo control is not considered unethical.~~ **As early symptomatic treatment of PD may provide some form of neuroprotection, the use of a placebo-control in long-term trials may be considered unethical therefore short-term studies are recommended.**	Important The justification for the use of a placebo-control is not the slow progressive course of the disease; rather it is the belief that delaying symptomatic treatment may not adversely affect long-term prognosis. However, data suggests that early symptomatic treatment of Parkinson's Disease (PD) may in fact provide some form of neuroprotection [The Parkinson Study Group, 2004 (ELLDOPA)]. Therefore it is considered that the use of a placebo-control should be restricted to short-term studies.	There is a point here. The justification for the use of a placebo-control is stated the sentence before given highly variable motor symptoms in the absence of placebo it may be impossible to distinguish between these spontaneous variability and a genuine treatment effect. It is agreed that long term placebo control is unethical but 6 months is not considered long term. That early symptomatic treatment of PD may provide some form of neuroprotection is at discussion and debatable. **The sentence is deleted without loss of the messages**.
EFPIA - line 133	How to interpret "demonstrate a similar or better benefit/risk"? Should the trial be powered to demonstrate statistically significant superiority, or non-inferiority, of the test drug versus comparator, or is a numerical comparison acceptable? Please clarify.	This is subject of debate in the EU. In the presence of placebo the benefit of two active compounds versus placebo and their relative efficacy may be assess based on clinical judgement. On could argue that non-inferiority may not have to be proven in a formal sense although such study should be large enough so that such assessment can be made i.e. the confidence intervals for the difference between the two active compound should not be that broad that no assessment can be made. For this reason the statisticians prefer to be clear and prefer that non-inferiority is established formally.
EFPIA - line 136 It is suggested that this guideline should not mandate the investigation of treatments	Critical Line 63 states that "In general, a patient with early stage PD will start with dopamine-agonists." The section beginning on line 136 describes the	This heading is wrongly interpreted. It was just a introductory remark introducing the next sections.

for PD in this population (patients currently receiving L-Dopa as monotherapy). It should be recognised that this population will decline over time and therefore alternative objectives needs to be considered, for example, symptomatic relief in patients currently receiving L-Dopa and dopamine-agonists.	design of clinical studies in patients currently receiving L-Dopa as monotherapy. It is considered that due to current clinical practice in the treatment of PD [Olanow, 2001], this patient population is decreasing in number and that in future years the recruitment of patients receiving L-Dopa monotherapy will become increasingly difficult. This view is supported by the statement in line 63, "In general, a patient with early stage PD will start with dopamine-agonists."	**No changes are deemed necessary.**
Schering-Plough Page 5/14 and 6/14, Section 4 Lines 136 through 147 Please clarify the difference between these two sections. *Symptomatic relief in patients with Parkinson's Disease on L-Dopa+* compared to Line 140 *Patients on L-Dopa+ with insufficient control of motor symptoms.*	We are unclear as to how these two sections differ.	The first section symptomatic relief in patients with Parkinson's Disease on L-Dopa+ refers to the situation were motor symptoms are quantitatively uncontrolled (hence the UPDRS may be improved) the second section motor fluctuations refer to qualitative changes e.g. ON/OFF. **No changes are deemed necessary.**
EFPIA - line 194 *Lundbeck 194*	What does "n=1 trials" mean? Please clarify. *EFPIA - line 194* It is not clear what is meant by (e.g. n=1 trials), and if 1 arm studies should be considered as an alternative trial.	Referred is to n **of** 1 trials design which is not an one arm study. The same patients receive treatment and placebo a multiple cross-over design. The response of the active treatment episodes is compared to that of the placebo episode. It is thinkable that in a trial were a limited number of subjects are subjected to such trial allows an extrapolation to a larger population. See for the principle: van Laar et al, "A double-blind study of the efficacy of apomorphine and its assessment in 'off'-periods in Parkinson's disease. Clin Neurol Neurosurg. 1993 Sep;95(3):231-5 **No changes are deemed necessary**
4.1 Design of the clinical studies **Patients with serious, unpredictable and rapid changing motor fluctuations**		

DeNDRoN No guidelines are given for the design of surgical trials e.g. need for sham surgery placebo or for comparison of drug treatments administered by different routes e.g. intraduodenal vs subcutaneous administration.		For sham surgery placebo see later. In the section Patients with serious, unpredictable and rapid changing motor fluctuations it is clearly stated that for proving efficacy randomised blinded comparative studies are needed showing a reduction of the motor fluctuations. This may either be an placebo add-on setting or conventional therapy with conventional routes of administration. **The text is clarified**.
4.1 Design of the clinical studies **Therapies aimed to modify disease progression: Treatment aimed to delay disease progression**		
Page 7/14, Schering-Plough Section 4 Lines 203 through 207 We suggest adding " the sole " in front of "…primary efficacy variable…" so the sentence reads: "*The reduction in L-Dopa+ doses as **the sole** primary efficacy variable is not recommended".(emphasis added)*	In the middle of the paragraph it is stated…*Primary efficacy variable should be time to late motor complications as pre-specified in the protocol. **The reduction in L-Dopa+ doses as primary efficacy variable is not recommended**.(emphasis added) However, it is necessary to take into account L-Dopa+ reductions when evaluating other efficacy variables in the light of these reductions. New study designs concerning postponing late motor complications may be developed but should be justified.*	As long as it is unsettled to which extent the motor complications are attributed to L-dopa therapy or disease progression, the reduction on L-dopa can not be considered efficacy parameter for evaluating a delay in disease progression. **No changes are deemed necessary**
H. Lindbeck A/S line 210 Design types such as the delayed start design or slope divergence are not mentioned. We suggest it to be mentioned here.		This section outlines general principles and is not advocating one specific study design above another. The value of one specific design above an other remains to be established. Here only the reservations with respect to the slope analysis are expressed. **There is no need for a revision.**
EFPIA - line 210 The number of trials evaluating products aiming to	Within the new section in the guidance on 'treatment aimed to delay disease progression' there is no	Further in vitro studies would violates the principle that a disease

delay disease progression is increasing. **In order to establish an impact on disease progression, distinction between symptomatic and disease modifying effects of a medicinal product has to be made**. There is however, no universal study design that can be recommended.	reference to the requirement to distinguish between symptomatic and disease modifying effects. It is recognized that there are no ideal study designs to unambiguously show a disease modifying effect, however it is felt that this point should be captured. A suggested rewording is thus proposed. In addition, comment on the validity of a delayed start study design would be of value, in addition to discussion on whether in vitro receptor studies would be sufficient to exclude symptomatic effect.	modifying claim will not be given if a delay in disease progression can not be correlated to an effect on the underlying pathophysiological process in a head to head study. **The text proposal is agreed and adapted accordingly.**
Dendron	The potential problems with the delayed start design as a way of distinguishing symptomatic and disease modifying effect should be discussed. (enclosed in press article by Clarke on disease modifying trial protocols).	See answers above.
PSI-217-223 Replace text with text from AD guideline (lines 522-542) as follows. "A hypothesis ~~of disease modification~~ seems most consistent with a statistical comparison of rates of change in clinical symptoms over time (slope analysis). Therefore, the change in UPDRS may be evaluated by a slope analysis. However, it should be taken into consideration that although it is known that the natural course of disease may be approximated with a linear model over time, it is yet	The requirement to show disease modification parallels that in the Guidance on Alzheimer's disease (AD), issued at the same time as the PD Guidance. The guidance on AD is more specific, so unless there is good clinical reason, replace the PD text with text based on the AD guidance (lines 522-542) to make the guidelines' content consistent.	It is intended that the text for in this guideline is as consistent with that of dementia,. However the linearity of the rate of disease progression in Parkinson's disease is even more debatable than in Alzheimer disease questioning the appropriateness of the slope analysis approach and emphasising the milestone events approach. **There is no need for a revision.**

unclear, whether a linearity assumption holds true in the situation of a clinical trial with an intervening (potentially disease modifying) treatment effect. In consequence it should be established that at two distinct time points the treatment effect in the pre-specified endpoints increases over time in a parallel group design. Such a study can be enhanced at the end of the trial with a phase of a randomized start or randomized withdrawal design. The magnitude of the treatment effect in terms of established outcomes, is estimated based on the difference between placebo and experimental compound at study end. The possible disease modifying effect may be addressed by a slope analysis or by a survival design (e.g. time to progression to pre-specified clinical keystones of disease). Both approaches to establish a disease modifying effect have their drawbacks and may be further hampered by possible placebo response, differences in drop out rates and missing data in general, poor adherence to treatment, change of treatment response with course of disease, etc. Therefore the		

choice of primary analysis and the fulfilment of underlying assumptions and requirements should be justified in detail in the study protocol. It may be considered to perform both analyses, e.g. a survival analysis as primary and slope analysis as secondary."		
EFPIA - lines 208-245 Comment on what would be considered a qualified or acceptable biomarker would therefore be extremely helpful, together with criteria for validation that would meet regulatory requirements.	Line 234-235 states the biomarkers that <u>*are not*</u> adequate for demonstrating disease progression (SPECT-beta-CIT and PET-F-DOPA). Lines 242-243 state that "demonstration of an effect on the underlying pathophysiology of the disease by e.g. biomarkers" is required. Given the likely size and duration of trials necessary to demonstrate disease modification, and that this will require biomarker confirmation of slowing/arresting pathophysiological progression, it is important that there is confidence in the selected biomarkers.	Again as long as no disease/modifying claim is opted for a relationship between disease progression as measured clinically and the underlying pathophysiological process has not to be shown. For a disease/modifying claim this would be necessary. To day there is no accepted biomarker showing an effect on the underlying pathophysiological process. For acceptance of such marker it should be shown that treatment affects both disease progression and the underlying process to an extend that the effect on the biomarker is predictive for clinical outcome. This has to be established in long term studies were both are measured. So that such relationship can be evaluated. It is acknowledged that there are no accepted biomarkers for disease progression but as they can only emerge from such studies we have to start somewhere. **There is no need for a revision.**
EFPIA - lines 214-216 Early untreated PD (de novo patients): The goal is to slow the progression of motor symptoms by assessing change in UPDRS, or time to L-Dopa+/DA-agonists. The proposed trial duration should **<u>12 to 24 months</u>** ~~be sufficient long probably up to 24 months~~.	The above sentence from the guidance is not clear i.e. '*probably up to 24 months'*. When looking at studies with the currently available treatment, the placebo decline over time indicates than with an appropriately sized study, an effect could be seen as early as 12 months. This should be reflected in the guidance.	A study should be sufficient long to address its objectives. Whether can be done in 12 months or 24 months depends on natural course of the disease, severity of the disease at entry, the potential treatment effect and which effect size is considered clinically relevant. The main message here is that the study should be sufficiently long. It is anticipated that a study lasting 24 months may probably more successful in this respect than a study of 12 month duration. **There is no need for a revision.**
EFPIA - lines 216-223 A repeated measure model	A slope analysis is proposed for change in UPDRS.	The EFPIA acknowledges the hesitations with respect to the slope

(e.g. mixed model for repeated measures) would be more adapted in this setting.	UPDRS change is often very far from being linear, thus a slope analysis is not adapted.	analysis and suggests another analytic method. Instead of adapting the text as suggested it will be added: ***"Given these reservations with respect to the slope analysis, alternatives analysis, if justified, may be more appropriate."***
EFPIA - lines 224 "Further caveats concern the use of time to L-Dopa+ which requires highly standardized assessments".	Clarity is requested on the standardised assessments required when using "time to L-Dopa+" as the primary outcome measure.	If studies aimed to delay disease progression include patients with early Parkinson's disease time to addition of L-dopa may be considered as a milestone event. This however would require a operational definition of the event and assessment of these at regular time intervals. It should not be left at the discretion of the investigator.
EFPIA - lines 226-229 "Stable treated PD: the goal is to slow further decline of motor impairment, progression of disability, prevent motor complications and prevent non-motor complications. Studies may demand 2-5 years. Key outcomes measurements for this stage could be **time to motor complications or** the emergence of so-called axial symptoms: e.g. freezing of gait, loss of balance or Hoehn & Yahr stage III".	"Stable treated PD: the goal is to slow further decline of motor impairment, progression of disability, prevent motor complications and prevent non-motor complications. Studies may demand 2-5 years. Key outcomes measurements for this stage could be the emergence of so-called axial symptoms: e.g. freezing of gait, loss of balance or Hoehn & Yahr stage III". Within the above statement, it is recognised that the intention is not to give a fully prescriptive list of outcome measurements, however it is felt that "time to motor complications" should be reflected in the guidance.	As long as it is unsettled to which extended motor complications are attributed to L-dopa therapy or disease progression, the time to motor complication can not be considered an milestone event for a claim of delay in disease progression. **No revision needed.**
EFPIA - lines 234-237 "Biomarkers measuring the cerebral dopamine uptake (SPECT-β-CIT) or dopamine-receptor density (PET-F-dopa) cannot be considered sufficient surrogate biomarkers for	The above statement should be amended to make it clear that these biomarkers are considered to relate to the course of disease, however they have not been validated for correlation to treatment effect i.e. they can not be considered as surrogate measures of efficacy.	**The text proposal is agreed and adapted accordingly.**

measuring disease progression. Although these are biomarkers for nigrostrial function it is not established that they **correlate to a** ~~result in~~ meaningful, measurable and persistent changes in clinical function". Simultaneous assessment of clinical outcome and biomarkers is recommended in order to evaluate whether both are causally associated and to assess the potential predictive value of a biomarker for clinical outcome. **These biological markers can however be used as supportive evidence of efficacy in pivotal trials, as a secondary measure to the validated clinical outcome measures.** If delay in disease progression is shown, this does not imply that a new agent is also a disease modifier. This requires the demonstration of an effect on the underlying pathophysiology of the disease by ~~e.g.~~ biomarkers **e.g. biochemical markers or neuroimaging measures**. Therefore for a disease-modifying claim a two-step procedure is foreseen, first a	In addition clarity is sought on the value of biochemical markers of PD i.e. alpha- synuclein. Within the above statement it should be made clear whether the biomarkers discussed in this guidance can be considered as sufficiently validated to act as supportive evidence of efficacy and therefore support a full claim of disease modification today. Additionally, guidance is required on whether these markers could be considered validated for use as primary endpoints in proof of concept studies. In relation to the above statement, it should be clarified that the first step towards a disease modification claim is based on showing a delay in the clinical measures of progression. In addition, it should be clarified that biomarkers of PD could include not only neuroimaging measures, but also biochemical markers (e.g. alpha- synuclein).	The value of. alpha- synuclein as biochemical a marker in PD is uncertain and has to be shown according the same principles as for the other biomarkers. See earlier comments. Again a disease modifying claim will only be warranted when the relationship between the biomarker and clinical delay of disease progression is established. This required long term studies where both the biomarker and disease progression is assessed and the biomarker is influence can be correlated to a meaningful change of clinical function. See earlier comments. The text proposal violates this principle en therefore is not acceptable. **The text proposal is agreed and adapted accordingly. However for the sake of clarity the following is also added":** **Therefore for a disease-modifying claim a two-step procedure is foreseen, first a delay in the clinical measures of disease progression should be shown, second an effect on the underlying pathophysiology process which correlate to a meaningful, and persistent changes in clinical function".**

delay in **the clinical measures of** disease progression should be shown, second an effect on the underlying pathophysiology process should be established.		
Biogen Idec and Vernalis-Line 13-15 lines 243-245 "For a disease-modifying claim a ~~two-step procedure is foreseen, first a delay in disease progression should be shown, second an effect on the underlying pathological process should be established.~~ **a delay in disease progression should be shown and an effect on the underlying pathological process could be established (subject to the availability of validated biomarker)."** *H. Lundbeck lines 241-245* The paragraph is unspecific, in particular how an effect on the underlying pathophysiology of the disease should be demonstrated as biomarkers are not available.	This statement is contradictory to the meaning of text included in lines 234-236 of this Guideline which states that the biomarkers measuring the cerebral dopamine uptake are not validated and cannot be considered sufficient surrogate biomarkers for measuring disease progression. As there are no validated biomarkers measuring changes in nigrostriatal functional anatomy it will be very hard to establish the effect of an investigational drug on underlying pathological process. Also, this requirement is at odds with requirements specified in EMEA 2006 MS guidance for making disease modification claims where clinical criteria alone are required.	This is partly a semantic discussion how disease modification is defined. Nevertheless this is relevant as it is used to support claims that are may not be justified In the MS guidance it is defined as a modification of the natural course of the disease. Here delay in disease progression and disease-modification are synonyms. It is not used to claim the one or the other. In Parkinson /Alzheimer disease modification has a neuroprotective connotation which needs further justification. A delay in disease progression not necessarily supports a disease modifying claim in the sense of neuroprotection. It is acknowledged that there are no validated biomarkers that could serve a surrogate endpoint up to now. However it is not excluded that in the near future validated biomarkers may be identified. **No revision is deemed necessary.**
4.1 Design of the clinical studies **Substitution of neuronal loss**		

DeNDRoN No guidelines are given for the design of surgical trials e.g. need for sham surgery placebo or for comparison of drug treatments administered by different routes e.g. intraduodenal vs subcutaneous administration.		See earlier. No recommendations can be given with respect to the surgical procedure let alone the feasibility of a sham surgery as the study design has not been settled yet. Probably alternatives to the sham procedure will be needed.
4.1 Design of the clinical studies **Treatment of cognitive dysfunction in Parkinson's Disease**		
Schering-Plough Page 8/14, Section 4 Line 254	There are dopamine markers currently being used which may be helpful in distinguishing different dementias. More guidance in this area would be helpful.	This is acknowledged but not relevant to mentioned here as the value of these techniques is still at discussion. **No revision is deemed necessary.**
Biogen Idec and Vernalis- Line 13-15 lines 255-256 PDD and Dementia with Lewy Bodies (DLB) are subsumed under the umbrella Lewy Body dementia ~~*with impaired α-synuclein metabolism.*~~	There is no hard evidence that all PDD and DLB have α-synuclein metabolism as their main substrate	Agreed. The text becomes: *"**PDD and Dementia with Lewy Bodies (DLB) are subsumed under the umbrella Lewy Body dementia*** ~~*with impaired α-synuclein metabolism."*~~
Biogen Idec and Vernalis- Line 13-15 lines 257-259 "In the early stages, PDD cognitive deficits are characterised by **impairment in** executive dysfunction, ~~impairment of~~ attention and	Various studies have shown that the loss of function in the same cognitive domains overlap in early PDD and AD patients so the distinguishing factors between early PDD and AD would rather be a presence of parkinsonian motor symptoms in PDD and early and progressive memory loss in AD. (Also refer to EMEA's Guideline on Medicinal Products for the Treatment of Alzheimer's Disease and Other	The company is correct. There are doubts whether the prerequisite of parkinsonian motor symptoms for the diagnosis PDD is adequate as this prerequisite is already in the definition. However, we will not challenge the current consensus. Ergo the text proposed is agreed i.e. : *"In the early stages, PDD cognitive deficits are characterised by **impairment in** executive dysfunction, ~~of~~ attention and working memory **that is substantiated by presence of major parkinsonian motor***

working memory **that is substantiated by presence of major parkinsonian motor symptoms. I**n contrast **the major feature of** ~~to~~ Alzheimer's disease **is a progressive memory loss from the beginning."**~~where memory loss is the major feature from the beginning~~	Dementias, section 4.1.3, lines 179-184 for a consistency).	***symptoms. I****n contrast* ***the major feature of*** ~~*to*~~ *Alzheimer's disease* ***is a progressive memory loss from the beginning."***~~*where memory loss is the major feature from the beginning*~~
Biogen Idec and Vernalis-Line 13-15 lines 267-268 For a specific claim of efficacy in PDD, efficacy should be shown on cognitive **measures** and AD*L*.	For a specific claim of efficacy in PDD, efficacy should be shown on cognitive and ADL.	Fine tuning. See next row.
EFPIA - lines 268 "… should be shown **<u>on cognition</u>** ~~on cognitive~~ and ADL"	There are some typos, or missing words that would need revision.	**Agreed and adapted accordingly.**
EFPIA - lines 270-273 Potential areas specific to depression in PD could be considered: • Whether or not depression is directly related to underlying pathological process of PD, or due to a diagnosis with a chronic and disabling illness, achieving stabilisation of PD symptoms is preferable prior to	The two sentences in this section do not do justice to this subject, given the prevalence of depression in Parkinson's Disease, and its associated morbidity. The statement that "it is still under discussion whether depression in PD can be separated from major depressive episodes" is a fair reflection, however, there are some specific comments that would be appropriate to include in the guidance.	Although this all is acknowledged the message is that for the time being depression in Parkinson is not considered a separate entity and hence an specific claim of treating depression in Parkinson's disease can not be warranted. The depressive symptoms in Parkinson disease are either diagnosed part of a genuine depression which would warrant treatment with a known antidepressant or diagnosed as belonging to Parkinson's disease and require fine tuning of the Parkinson treatment as stated in the first column. Point is that an isolated claim depression in Parkinson is considered a pseudo-indication .

embarking on treatment for depression, given that dopamine replenishment itself may improve depressive symptoms in PD. • The diagnosis of depression may not be straightforward, given that facial masking and bradykinesia can be confused with psychomotor retardation of depression. Additionally, in later stages of disease, fluctuating motor symptoms may be associated with mood swings, and patients may only fulfil criteria for Major Depressive Disorder at certain times. • Some drugs used to treat Parkinson's Disease may also be used as antidepressants e.g. MAO-B inhibitors such as selegiline. • Important safety considerations include the increased likelihood of sensitivity to CNS adverse events with antidepressants, and the risk of serotonin		**No revision is deemed necessary.**

syndrome with SSRIs combined with MAO-B inhibitors.		
Schering-Plough Page 8/14 Section 4 Lines 270-273 ***Treatment of depressive symptoms in Parkinson's Disease***	Since the Hamilton Scale was confirmed by the Parkinson Consensus Group to be a valid measure of Parkinson's Disease Depression the issue of using these scales should be evaluated and allowing treatment of depression in PD as a separate entity should be reconsidered.	See answer above
4.2 Dosage		
Biogen Idec and Vernalis-Line 13-15 lines 275-281 A sentence should be added acknowledging that titration may not be needed if outcomes of pivotal studies have justified that the drug does not need to be titrated over a period of time..	There is no evidence that the titration will be needed for novel, multimodal and non-dopaminergic agents like A2a antagonist.	This section does not require titration but givens guidance to deal with titration if applied i.e. how to define the optimal dose operationally and the need for fixed dose studies. It does not state that dose titration are required. This is covered by the first sentence it is **custom** but than take care of … **No changes are deemed necessary**.
EFPIA - lines 282-286 Titration of doses for individual patients according to response **as defined by the individual investigator** may lead to dose recommendations which are broad and vaguely described. These studies should incorporate randomised arms in which patients are titrated to ~~fixed doses which are~~ **the**	Important It is acknowledged that the criteria of an optimal effect and intolerance should be unambiguously defined in the study protocol. However, the design of a longer-term study with fixed doses of a new anti-Parkinsonian drug is not considered to be appropriate. Titration of doses for individual patients according to response is necessary: doses may need to be increased as the disease progresses over time however the lowest possible dose should be used in order to avoid any potential deleterious effects such as long-term motor complications.	***Agreed the text is adapted accordingly.*** Titration of doses for individual patients according to response **as defined by the individual investigator** may lead to dose recommendations which are broad and vaguely described. The lowest therapeutic dose is not agreed. This paragraph refers to dose-finding studies which are intended to determine the effective dose range including the lowest, optimal and maximal therapeutic range.

lowest therapeutic dose which is maintained for the subsequent maintenance period..		
5. ASSESSMENT OF EFFICACY CRITERIA		
Line no. + para no.	**Comment and Rationale**	**Outcome**
PSI 306-308 Perhaps specific reference could be made to time to event type analyses in this section	The recommendation to define a responder criterion may be reasonable if based on a quantitative variable (although one may argue that information is lost in this case). However, the paragraph as written now may discourage the use of time to event trials.	Responder is a general term for defining success and failure. It not necessarily requires a quantitative variable. The occurrence of an event is also a definition of success and failure. However as this apparently this may be misunderstood the following is added: **Success and failure may also be defined in terms of time to event depending of the study aim**
PSI 312 Delete "by responders" phrase.	The text states: "(e.g. degree of symptom relief from baseline experienced by responders)". Why consider responders - shouldn't the expected effect be considered in responders and non-responders combined?	This is correct the text is adapted accordingly i.e. "(e.g. degree of symptom relief ~~from baseline experienced by~~ , **difference in proportion of** responders)".
PSI 316	Some indication of how these efficacy variables are used to create endpoints or parameters to estimate would be helpful. For instance, change from baseline, average effect over time, slope analysis. Other secondary variables and associated endpoints/parameters should be referenced	Methods to assess efficacy primarily concern assessment scales not the precise definition of the primary endpoint. Here is dealt with in the previous section i.e. the degree of symptom reduction from baseline , responders. It is preferred not to be too specific as the precise definition of the primary variable depends on the aim of the study, severity of the disease of the patient included …etc. This would not only need full coverage of all study conditions but also allows no flexibility. ***No revision is proposed***
Schering-Plough Page 9/14 Section 5 Lines 319-325	Please provide guidance on what scales are recommended or may be used when the UPDRS is not appropriate.	No recommendation is given, as experience with the use of dyskinesia scales in confirmatory PD trials is limited. An option may be the AIMS but it is too early to recommend one scale above another.
EFPIA - lines 322	There are some typos, or missing words that would	***Agreed the text is adapted accordingly***

"… the UPDRS IV is not appropriate and ~~UPRS~~ **UPDRS** II is not acceptable…."	need revision.	
PSI lines 330-333 Some guidance on how to resolve this multiplicity would be helpful.	Scoring separately over ON and OFF periods creates a problem of multiplicity. For instance, would it be reasonable to look at a combined score initially and then at sub-scores?	No recommendation on dealing with multiplicity is given here as options a numerous and depend on the aim of the analysis. Referred is to textbooks. It is noted here that this section is on methods how to assess efficacy. Assessing motor symptoms during ON en OFF is more for verification whether a patient is in ON or OFF. When the effect of a treatment on motor symptoms is evaluated it should be clear that a patients with ON/OFF states in ON or OFF. Otherwise it may incorrectly be concluded there is a treatment effect. ***No revision is proposed***
Schering-Plough Page 9/14 *Section 5 Lines 334-337 For both, assessment of motor function and/or "ON"-, "OFF"-time with/without dyskinesias, the evaluation by the patient by means of a diary is needed. Patient's diaries scoring the type of dyskinesias (disabling/non-disabling) over predefined periods on pre-specified days during the trial are recommended.*	Need additional guidance on definition of "*disabling/non-disabling*". There may need to be some standardization of what is "*disabling or non-disabling."*	An operational definition of disabling/ non-disabling dyskinesias should be in the study protocol. ***No revision is proposed***
6. SELECTION OF PATIENTS		
Line no.[2] + paragraph no.	**Comment and Rationale**	**Outcome**
6.1 Study population		

[2] Where applicable

Biogen Idec and Vernalis-Line 13-15 lines 348 "Especially in **early** ~~beginning~~ PD there may be diagnostic…	None	Early is indeed better i.e. *"Especially in **early** ~~beginning~~ PD there may be diagnostic…"*
DeNDRoN	The possibility of building in a dopamine transporter (DAT) scan as a baseline to avoid inclusion of SWEDDs could be considered.	This is acknowledged but not relevant to mentioned here as the value of these techniques is still at discussion.
6.2 Study design		
EFPIA - lines 361-363 ~~As misclassifications, especially in early-stage PD, occur frequently this should be taken into account when the number of patients to be recruited in estimated~~. **It is recommended that the number of patients recruited be increased to allow for misclassifications which occur frequently, especially in early-stage PD.**	It is suggested that the reference to misclassifications is clarified.	The text proposal is better and agreed. The text is adapted accordingly. Clinical experience confirms that in early stages and mono symptomatic presentation the distinction between Parkinson's disease, MSA, PSP can be difficult. See also the introduction.
PSI lines 361;368;371 Delete sample size and stratification text, or explain why these specific aspects of E9 are reproduced here.	ICH E9 (Statistical Principles) is referenced so it is not clear why "sample size" and "stratification factors used for randomisation" are specifically highlighted in lines 361 and 371 respectively since these topics are adequately covered in ICH E9.	Sample size is mentioned here in order to emphasise that misclassifications should be accounted for. The term stratification is used her in the context of the primary analysis i.e. the primary analysis should take into account the usual stratification factors as well what is specific for Parkinson trials i.e. concomitant anti-Parkinson medication and changes in medication during the trial. **There is no need for revision**
PSI lines 361-363	Text states that misclassified subjects should be taken into account when the number of patients to be	This interpretation is correct.

Please clarify the impact of misclassified patients on the sample size and analysis sets.	recruited is estimated. We assume that this means that the expected number of misclassified patients is estimated and that the sample size is increased accordingly. However it is not clear whether these misclassified patients should then be excluded from the analysis sets. If not, then what would be the rationale for adjusting the recruitment?	Misclassifications will only be clear after a while and adds to the variability and thus sensitivity of conclusive results. **See adaptation agreed before.**
PSI line 367 Reference 4.1.	Section 6.3 should reference section 4.1, since section 4.1 contains some of the statistical detail.	**Agreed.**
PSI lines 367 - 373 Reference the slope analysis and provide more detail in relation to the statistical analysis	More detail on the statistical analysis of the slope analysis contained in section 4.1 would be helpful.	Referred is to the answer in *PSI-217-223*
PSI lines 367 - 373 We do not suggest more detail here, but suggest that the CHMP's Missing Data PtC is updated to include more information on how to handle therapeutic indications which naturally have high withdrawal rates.	In PD studies, patient withdrawal can be quite high in percentage terms. Some therapeutic specific guidance on approaches to handle such quantities of missing data would be helpful.	The message is well taken. However in our experience compared to other areas, in PD studies patient withdrawal is rather limited even in percentage terms.
PSI lines 369-370 Some clarification regarding evaluating the effect in the maintenance period would be helpful.	Some further guidance on evaluating the effect in the maintenance period would be helpful here. For instance, is it the average effect during the maintenance period that is of primary importance, or the effect at the end of the maintenance period, or some other measure or timepoint.	Referred is to the answer given earlier PSI-316
PSI lines 369-370 Some clarification on how changes to concurrent co-medications are to be taken	The text states that the "primary analysis should take into account…. the use of anti-Parkinson drugs at baseline and changes in concurrent medication during	It is acknowledged that this is not simple. However it should be clear whether an observed treatment effect observed can be attributed to the new compound or changes in concurrent medication.

into account in the analysis would be helpful. For instance, as part of a responder definition - where certain pre-specified changes to concomitant PD medication would constitute a treatment failure. Changes in concurrent medication could perhaps be investigated in robustness analyses to the primary analysis rather than in the primary analysis itself.	the trail in particular". It is not clear from a statistical perspective how adjustment can be made for post-baseline covariates as this has the potential to introduce bias (since they cannot be guaranteed to be independent of the treatment received). Changes in concurrent medication could perhaps be investigated in robustness analyses to the primary analysis rather than in the primary analysis itself.	Indeed after a patient has reached the maintenance period where the doses test agent and concurrent medication is supposed to be optimal changes in dose of either medication may be considered treatment failure.
PSI 395-396	Should pharmacokinetics be explored in an elderly population or is it sufficient to establish it for your volunteers? Also, the statement about studies in renally or hepatic ally impaired patients is rather vague.	Referred is to the interaction guidance. As PD in general is a disease of the elderly it appears wise to evaluate the PK in elderly volunteers or patients
7. STRATEGY/DESIGN		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
EFPIA - lines 419-420 An additional comment that relates to specific AEs pertaining to certain drug classes would also include episodes of "Sudden Onset of Sleep" with synthetic dopamine agonists.	Comment on specific interventions that may be acceptable with respect to contextualising/ characterise these events would be helpful e.g. independent expert review panel.	This paragraph is just an example of a potential class effect and should be read in conjuncture to the paragraph above.

[3] Where applicable

REFERENCES (SCIENTIFIC AND/OR LEGAL)		
Line no.[3] + paragraph no.	**Comment and Rationale**	**Outcome**
PSI 507/508 and 520/521 Remove duplicate and re-order references alphabetically from 509 onwards	Duplicate reference for Wesnes *et al* and references after line 509 are not in alphabetic order	The corrections are made.