SCIENTIFIC DISCUSSION

I. SCIENTIFIC DISCUSSION

1.1. Introduction

DaTSCAN contains the active ingredient [^{123}I] ioflupane (also known as [^{123}I] FP-CIT), which is a radioiodinated cocaine analogue. The product is an ^{123}I-labelled synthetic tropane derivative that binds with high affinity to the pre-synaptic dopamine transporter protein (DAT) located on the presynaptic nerve endings (axon terminals) in the striatum. The axon terminals are projections of the dopamine neurones in the substantia nigra. Therefore, DaTSCAN acts as a biomarker of loss of functional dopaminergic neuron terminals (e.g., for detection of the striatal degeneration that is present in Parkinson's disease [PD]). It has been developed as a dopamine transporter-imaging agent for single photon emission computed tomography (SPECT).

The efficacy of DaTSCAN in detecting the loss of functional dopaminergic neuron terminals in patients with parkinsonian syndromes (PS) has been demonstrated. Two presentations of DaTSCAN (2.5 ml and 5.0 ml) are registered in the European Union, the former since 2000.. The current indication is as follows:

"DaTSCAN is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain Parkinsonian Syndromes (PS), 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 this present application, the MAH is proposing to extend the indication to use DaTSCAN as an adjunct to the clinical diagnosis of Dementia with Lewy Bodies (DLB) as follows:

"*to help differentiate dementia with Lewy bodies from other forms of dementia*".

Rationale for the proposed change

DLB, the second most frequent cause of degenerative dementia in elderly adults (after Alzheimer disease), is a neurodegenerative disorder associated with abnormal structures (Lewy bodies) found in certain areas of the brain. Lewy bodies (LB) are intracytoplasmic, spherical, eosinophilic neuronal inclusion bodies. The areas of predilection for LB are brainstem, subcortical nuclei, limbic cortex and neocortex and their accumulation results in a loss of functional dopaminergic neuron terminals in the striatum[1].

In 1996, an international workshop published consensus guidelines for the clinical and pathologic diagnosis of DLB[1] [International Consensus Criteria (ICC)], revised in 2005[2] to describe the criteria for the clinical diagnosis of DLB. The revised criteria already include low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging" as a suggestive feature. Indeed, if one or more of the suggestive features is present in the presence of one or more core features (fluctuating cognition, recurrent visual hallucinations and spontaneous features of parkinsonism), a diagnosis of probable DLB can be made". The ICC for probable DLB, which have been prospectively validated on the basis of post-mortem data[3], have demonstrated a sensitivity of 83% and a specificity of 95%.

The diagnosis of DLB requires thorough clinical assessment including a detailed medical history (from patient and carer) and a full mental state, cognitive and physical examination (including a

[1] McKeith IG, and al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies. Neurology 1996;47:1113-1114
[2] McKeith IG, and al. Diagnosis and management of dementia with Lewy bodies. Neurology 2005;65(12):1863-72
[3] McKeith IG, and al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology.2000a;54:1050-8

neuropsychiatric examination with emphasis on eliciting core features) by a clinician experienced in dementia. The rationale of this new diagnostic extension put forward by the MAH is that DLB patients have specific treatment requirements and functional disabilities that differ from those of other forms of dementia and that require specialised, often multi-disciplinary treatment.

Fluctuating cognition, hallucinations and/or sleep disorders, which are infrequent in Alzheimer disease (AD) and vascular dementia (VaD) patients, can be particularly disturbing to the DLB patient and their family members (or carer). DLB patients may deteriorate more quickly and/or require more intensive and more specialised care than do AD patients. This implies intense training of the family member(s) and/or in a nursing home of the caregiver(s) involved.

The importance of correct diagnosis lies also in the pharmacological management. DLB patients often respond well to cholinesterase inhibitors which have been shown to substantially improve both cognitive and neuropsychiatric symptoms[4]. In DLB patients, severe sensitivity reactions (in 50% of the patients) upon administration of D2 antagonist neuroleptics are associated with significantly increased morbidity and a 2- to 3-fold increase in mortality[5]. Sensitivity reactions to the newer atypical anti-psychotics have also been documented and the above recently published treatment guidelines recommend that even these newer generation neuroleptics should be avoided whenever possible. It should be noted, however, that no typical or atypical neuroleptic is formally indicated in dementia and all atypical neuroleptics have a warning in their SPC about the increased mortality in this population. Recent studies show that some DLB subjects may benefit from levodopa treatment of extrapyramidal motor symptoms, although this should be titrated carefully and be administered at the lowest possible dose to minimise side effects (most notably visual hallucinations or increased confusion).

3.2. Non clinical aspects

As stated, ioflupane binds with high affinity to striatal pre-synaptic dopamine transporter protein (DAT) in animals and in humans and acts as a biomarker for loss of functional nigrostriatal neuron terminals.

In this variation it is proposed to expand the current indication to use DaTSCAN as an adjunct to the clinical diagnosis of DLB. DaTSCAN will be administered by the same route of administration (intravenous injection) used in the currently approved indication, and targeted to the same brain region (dopamine transporters in the striatum). The administered pharmacological and radioactive doses will be the same, and the mechanism of action is expected to be the same, and therefore the nonclinical documentation provided in the earlier application is also relevant to the current application.

Recently published studies in animals (primates and rats) have indicated a possible interaction between ChE inhibitors and the availability of the DAT in the brain. This might constitute an efficacy issue in imaging with DaTSCAN if these drugs bind to or in other ways modulate the availability of the DAT. Possible interactions between the ChE inhibitor rivastigmine used for DLB patients and DaTSCAN have therefore been evaluated.

Pharmacodynamic drug interaction study

The MAH investigated the effect of rivastigmine (a ChE inhibitor commonly administered to patients with DLB) on the uptake and retention of ioflupane via the dopamine transporter in brain tissues (striatum, cerebellum and hypothalamus) of Wistar rats *in vivo*.. The CNS stimulant methylphenidate was used as a positive control in the study, since it is known to reduce DaTSCAN striatal uptake by binding strongly to the DAT (i.e. by competing with ioflupane binding to the DAT). The dose of methylphenidate (10 mg/kg b.wt.) and the time interval between the oral administration of

[4] McKeith and al. Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. Lancet 2000a; 356:2031-6

[5] McKeith, and al. 1992; Ballard and al. 1998

methylphenidate and injection of DaTSCAN (2 hours) were selected according to the known kinetics of striatal uptake of orally administered methylphenidate to rats.

Three groups of rats were each given an oral dose of one of the following:

1. Methylphenidate (10mg/kg/bw, n=4) - positive control; known to reduce ioflupane striatal uptake by competitively binding to the DAT.
2. Rivastigmine (2.5mg/kg/bw, n=5) – the test agent.
3. Saline (1.2ml/kg/bw, n=5) – vehicle control

An intravenous bolus injection of DaTSCAN (100μCi, 3.7 MBq; 4ng of ioflupane) was administered 40 minutes after the methylphenidate and 2 hours after the rivastigmine and saline.

All rats were anaesthetised with a mixture of xylazine/ketamine (2/1: v/v; 0.1 ml/100 g b.wt. intramuscularly) before an intravenous injection of DaTSCAN in the tail vein was administered The use of anaesthetics was assumed not to influence the outcome of the study since the test substance (rivastigmine) was given 2 hours before anaesthesia. Therefore, based on known kinetics of rivastigmine in the brain, it had already exerted its effect on the DAT at the time anaesthetics were given.

At 2 hours after administration of DaTSCAN, the animals were sacrificed and samples of selected brain tissues (striatum, hypothalamus, occipital cortex and cerebellum) were excised, weighed and the ^{123}I radioactivity was measured in a gamma counter.

The occipital cortex and the cerebellum are both devoid of DAT binding sites. The uptake in the occipital cortex or in the cerebellum is therefore often taken to reflect non-specific uptake. The numerator in these ratios (striatum–cerebellum) and (striatum–occipital cortex) i.e. total uptake minus non-specific uptake, reflects specific DAT-mediated uptake in the striatum. The ratios (striatum–cerebellum)/cerebellum and (striatum–occipital cortex)/occipital cortex i.e. ratios of specific-to-non-specific uptake, when stable in time, are assumed to be proportional to the number of available DAT binding sites. Similarly, the ratio (hypothalamus–occipital cortex)/occipital cortex is assumed to reflect serotonin transporter (SET) mediated uptake in the hypothalamus versus non-specific hypothalamic uptake (the hypothalamus expresses SET to which DaTSCAN also binds, and the hypothalamus does not express DAT).

The ratios (striatum–cerebellum)/cerebellum and (striatum–occipital cortex)/occipital cortex were found to be statistically significantly lower ($p<0.05$) in the methylphenidate group versus the saline group and the rivastigmine group. The same ratios were not statistically significantly different between the saline group and the rivastigmine group. No statistically significant effect ($p<0.05$) between the groups for the ratio (hypothalamus–cerebellum)/cerebellum was detected.

3.3 Clinical aspects

DaTSCAN is approved for use as an intravenous single dose between 111 and 185 MBq activity, and this dose is also recommended for the new claimed indication. No additional clinical pharmacology studies have been performed for this application because distribution, metabolism and excretion of DaTSCAN are considered the same as in the previous population and because the aim being still to visualize the loss of functional dopaminergic neuron terminals.

3.3.1 Clinical efficacy

Clinical Studies

The clinical development program of DaTSCAN included efficacy data obtained from 2 investigator-initiated studies, so called “proof-of-concept studies”, and 1 pivotal, clinical open phase 3 study (PDT301) performed by the MAH in adults who presented DLB or other forms of dementia depending of study and in healthy volunteers (control subjects).

3.3.1.1. Proof-of-concept studies

There were 2 proof of concept studies designed to assess whether DaTSCAN SPECT imaging for DLB is a useful clinical diagnostic marker for discriminating DLB from Alzheimer's disease (AD). Subjects diagnosed with DLB, AD, Parkinson's disease (PD) and similarly aged controls were enrolled into both studies. In the Newcastle study, patients were also recruited with Parkinson's disease with dementia (PDD).

SPECT (Single-Photon Emission Computed Tomography) imaging was undertaken after a bolus intravenous injection of 150-185 MBq of DaTSCAN. Images were evaluated on-site using region of interest based analysis (ROI) and a blinded visual qualitative assessment of all images, undertaken by 3 readers in the "Middlesex study" and by 3 readers in the "Newcastle study". The images were independently randomised and blinded from clinical data before being presented to each reader. In both studies, images were graded independently by each reader and a consensus taken if there had been no complete agreement between all readers.

- ***Newcastle Study (2000/2002) O'Brien J. Dopamine transporter loss visualised with FP-CIT SPECT in Dementia with Lewy bodies. Archives of Neurology 2004;61:919-925.***

Study design

This was a cross sectional study of cohorts of patients and similarly aged controls. Subjects underwent a detailed physical, neurological and psychiatric examination. The standard of truth was the clinical diagnosis determined by consensus between three clinicians (1 psychiatrist and 2 neurologists). SPECT imaging was undertaken using a triple-headed rotating gamma camera 4 hours after a bolus intravenous injection of 150 MBq of DaTSCAN.

This study pursued two aims:

1.- validation of the International Consensus Criteria (ICC) for the clinical diagnosis of DLB
2.- assessment of the relationship between DaTSCAN image findings and the clinical diagnosis.

Study population

The number of subjects in this study was 164 subjects: AD (NINDS/ADRDA National Institute for Neurological and Communication Diseases and Society and the Alzheimer's Disease and Related Disorders Association criteria) (n=34; mean age 78.9), PD (UK Brain Bank criteria) (n=38; mean age 75.6), DLB (ICC 1996) (n=23; mean age probable DLB 75.9), PDD (International Consensus Criteria) (n=36; mean age 72.1) and elderly control subjects (n=33; mean age 74.8).

Endpoints

Semi-quantitative analysis of DaTSCAN uptake using ROI based analysis in the caudate, anterior putamen and posterior putamen. The uptake was normalised to the occipital lobe to account for non-specific binding.

Statistical analysis

Diagnostic discrimination (sensitivity, specificity, positive predictive value and likelihood ratios) were calculated against the clinical diagnosis for separation of DLB, PD and PDD from controls and AD subjects using both ROI analysis and visual ratings. DaTSCAN uptake between groups using analysis of variance (ANOVA) with post-hoc Gabriel tests.

Results

The cohort of patients originally stemmed from a UK Medical Research Council (MRC) study established in Newcastle in 1995 to evaluate the clinical and pathological characteristics of patients with DLB. Interim results of the MRC study (supportive study) were published. In the 50 cases having reached autopsy, the ICC criteria for "probable DLB" could be prospectively validated on the basis of histopathological findings. Twenty-six clinical diagnoses of DLB, 19 of AD, and 5 of VaD were made. At autopsy, 29 DLB cases, 15 AD, 5 VaD, and 1 progressive supranuclear palsy were identified. The sensitivity, specificity and positive predictive value (PPV) of the clinical diagnosis of probable DLB in this sample were 83%, 95% and 90%, respectively, with autopsy as the absolute standard of truth.

Based on clinical diagnosis being interpreted as the standard of truth, both ROI analysis and visual ratings of DaTSCAN provided the following sensitivity and specificity between DLB and AD:
ROI: sensitivity 78%, specificity 94%;
visual ratings: sensitivity 78%, specificity 85%.
As expected, neither ROI analysis nor visual ratings could differentiate DLB from PD and PDD.

The multi-reader κ statistic for agreement between the 5 readers was 0.88 ± 0.02. The degree of agreement between each reader and the final consensus rating was also calculated (κ values for each individual reader were 0.91, 0.94, 0.91, 0.91 and 0.93).

- ***Middlesex Study (1996/1999) Walker Z. Differentiation of dementia with Lewy bodies from Alzheimer's disease using a dopaminergic presynaptic ligand. J Neurol Neurosurg Psychiatry 2002;73:134–140***

Study design

This was a proof-of-concept study with a first cross-sectional phase and a second, longitudinal phase.
The aim of the first stage was to compare DaTSCAN radio-uptake ratios in the caudate nucleus, anterior and posterior putamen as determined by semi-quantitative, ROI-based image assessment in patients with the clinical diagnoses of DLB, PD and AD and in controls. The baseline clinical diagnosis as established by an old-age psychiatrist following a comprehensive clinical, neurological and neuropsychiatric examination and based on internationally accepted diagnostic criteria served as reference standard for this cross-sectional study phase.
The aims of the second stage of the study were to determine the sensitivity and specificity of the following:

1) the ROI-based semi-quantitative analysis of DaTSCAN radio-uptake ratios in the caudate nucleus, anterior and posterior putamen when compared to the neuropathological diagnosis at autopsy as the standard of truth
2) the visual assessment of the DaTSCAN images analysed by 3 readers (who were blinded to all clinical information) when compared to the neuropathological diagnosis at autopsy as the standard of truth
3) the clinical diagnosis (reference standard of the cross-sectional study phase) when compared to the neuropathological diagnosis at autopsy as the standard of truth.

Study population

The total number of subjects in this study was 80 subjects meeting criteria for AD (NINDS/ADRDA criteria) (n=17; mean age 78.0), PD (UK Brain Bank criteria) (n=19; mean age 64.9), DLB (ICC 1996) (n=27; mean age probable DLB 77.3), corticobasal degeneration (n=1) (cross-sectional diagnosis) and older control subjects (n=16; mean age 66.6).

Statistical analysis

ANOVA and Student's t-test were used to assess for differences between the different groups (DLB, AD, PD and controls) in the DaTSCAN binding within the caudate nuclei and anterior and posterior putamen regions. Relationships between various clinical variables and uptake ratios were explored using Spearman's rank correlations for ordinal data. Diagnostic discrimination between DLB and other dementias (sensitivity and specificity) was determined using the results of both the ROI-based and visual assessments.

Results

DaTSCAN regional uptake (semi-quantitative method)

Both the DLB and PD groups had significantly lower radioactivity uptake in all striatal areas than the AD group and controls (ANOVA: $p<0.001$, contralateral and the ipsilateral caudate nucleus and anterior and posterior putamen). There were significant differences between DLB and AD, and DLB and controls for all ipsilateral and contralateral binding measures ($p<0.001$).

Visual assessment of scans

The agreement between the independent assessments of the specialist in nuclear medicine, the old-age psychiatrist and the neurologist was estimated by κ values, which were 0.85, 0.89 and 0.90. The visual rating was compared with the semi-quantitative results by defining as "abnormal" any scan with contralateral posterior putamen binding which was more than two standard deviations below the mean of the controls (<3.02). The consensus visual rating (two or all three raters in agreement) and the semi-quantitative rating gave the same result (normal or abnormal scan) in 72/79 scans (91%), with κ 0.82.

Autopsies

The aims of the second stage of the study were to compare the results with the neuropathological diagnosis at autopsy as the standard of truth. Analysis of the 17/80 *post mortem* data available showed a sensitivity of DaTSCAN SPECT imaging of 100% with semi-quantitative rating (ROI) and 86% with visual rating, and a specificity of 90% and 80%, respectively, compared to the *post mortem* autopsy diagnosis.

The values for the clinical diagnosis were 86% for sensitivity and 30% for specificity. This marginal specificity might be explained by the fact that the subjects participating were all recruited between 1996 and 1999, a time period in which the ICC criteria were first introduced and being evaluated and in which clinical assessment scales facilitating the detection/absence of fluctuating cognition were not yet available. Furthermore, since the Middlesex study recruitment period predated the ICC, it relied solely upon the clinical diagnosis of a single investigator and did not adopt the Consensus Panel approach used both in the Newcastle studies and in the pivotal study PDT301. This 3-way consensus method has previously been shown to have high validity against neuropathological diagnosis. In light of the Consensus Panel approach, the reliance on a single clinician to establish diagnosis was a methodological weakness in the Middlesex study, which resulted in suboptimal diagnostic accuracy.

3.3.1.2. Confirmatory study PDT301 (2003/2005)

Study design

This was a phase 3, multi-centre, open-label, non-randomised, single dose clinical study to assess the diagnostic efficacy and safety of DaTSCAN in subjects with DLB.
The primary objective was to determine the diagnostic efficacy of the visual assessment of DaTSCAN SPECT images in differentiating between "probable DLB" and non-DLB subjects when compared to the clinical diagnosis established by a consensus panel (CP) as the "standard of truth". Secondary objectives included determining the positive and negative predictive values.
The absence of structural abnormalities in the basal ganglia had to be ruled out by cerebral magnetic resonance imaging (MRI) or computed tomography (CT) imaging to be performed within 6 months prior to screening and the results had to be negative for vascular abnormalities indicative of infarction in the region of the basal ganglia.
The injection of DaTSCAN was open but it was planned that clinical diagnosis and image analysis were blind.

Methodology

For the efficacy assessment, the results of the DaTSCAN image analysis were compared to the clinical diagnosis.

Study population

The study population consisted of demented subjects (between 55 - 90 years of age) with features of probable or possible DLB and subjects with features of non-DLB (e.g., AD or VaD). The DLB subjects were selected for screening from movement disorder clinic databases, dementia services, memory clinics, and other general neurology clinics. The distribution of evaluable DLB and non-DLB subjects was assessed on an ongoing basis during the study as determined by the clinical diagnosis of the on-site physician.
The subjects presented positive assessment for dementia in accordance with the Diagnostic and Statistical Manual of Mental Disorder – Fourth Edition (DSM-IV) criteria and fulfilled at least one of the following: the ICC for probable or possible DLB, the NINCDS-ADRDA for AD, or the National Institute of Neurological Disorders and Stroke - Association Internationale Pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) for VaD. PDD patients were excluded (dementia occuring at least one year after PD diagnosis).

Clinical diagnosis and "standard of truth"

The clinical diagnosis was established using the ICC and based on a standardised and comprehensive clinical and neuropsychiatric evaluation. The "standard of truth" was the clinical diagnosis of DLB ("probable" or "possible") versus non-DLB (probable or possible AD, probable or possible VaD) established by an independent CP (ICP) consisting of 3 internationally recognised experts in the diagnosis of dementia and in DLB in particular. Indeed, 2 of the ICP members had a leading role in the Newcastle study and were intrumental in the prospective validation of the original ICC against post-mortem (see Introduction). The CP itself was validated in the Newcastle study, where the sensitivity was 83% (24/29 patients) and specificity was 90% (18/20 patients) - in this calculation both "probable" and "possible" DLB patients are assumed to be DLB patients. In addition, retrospective data from 10 subjects who had been diagnosed with DLB or AD by autopsy were given to the 3 Consensus Panel members used in study PDT301 (who were blinded to these patient's autopsy diagnosis), and they correctly diagnosed all of these patients.

DaTSCAN SPECT imaging

DaTSCAN SPECT images were obtained as recommended in the SPC. The images were acquired using a multi-headed (2- or 3-headed) gamma camera and imaging lasted approximately 40-60 minutes.

Images were evaluated at the independent image review centre (IRC) in Oslo, Norway, as part of a blinded image evaluation (BIE) performed by 3 independent readers (nuclear physicians with expertise in neuroimaging). Images were evaluated both visually and by a semi-quantitative assessment (ROI). During visual assessment, each of 3 blinded readers classified the images as normal, abnormal or other (an image that could not be assigned to one of the aforementioned classes) described below:

Normal images: Normal images were characterised by uptake of the tracer in both right and left putamen and caudate nuclei. The image was largely symmetrical with approximately equal levels of uptake on both left and right sides. Activity was contained close to the centre of the image forming 2 crescent shaped areas of uptake.

- Abnormal image type 1: Uptake is asymmetric with normal or almost normal putamen activity in 1 hemisphere and a more marked change on the other side.
- Abnormal image type 2: Uptake was significantly reduced in the putamen on both the right and left sides. Activity was confined to the caudate nuclei and forms 2 roughly symmetrical, circular areas.
- Abnormal image type 3: Uptake was virtually absent from both putamen and caudate nuclei on each side of the brain resulting in a significant reduction in contrast and the visualisation of background activity throughout the rest of the image.
- Other: Option provided if an image could not be assigned to any of the categories above.

The semi-quantitative assessment was a ROI-based analysis to determine the striatal DAT density calculated as the ratio of total specific striatal activity/non-specific activity. The striatal ROI data were analysed by 1 reader to examine the whole striatal, caudate, and putamen uptake in each hemisphere. Analysis of the co-primary efficacy endpoints, sensitivity and specificity, was solely based on the division of the above classes into normal or abnormal based on the result of the BIE. The 3 independent blinded readers interpreted the DaTSCAN images individually, with the images being presented to the readers in random order. The readers were blinded to the subject's personal and clinical information except for the subject's age. Age is required for appropriate evaluation of the SPECT images because with increasing age, the nigrostriatal DaTSCAN uptake decreases and the non-specific uptake increases due to overall decreased circulatory capacity.

Efficacy variables

The *co-primary efficacy endpoints* were sensitivity and specificity.

Table 5 Calculation of Specificity, Sensitivity, Accuracy, PPV, and NPV

Standard of Truth (Clinical Diagnosis of the CP)	Evaluation of DaTSCAN SPECT Images		Row Total
	Abnormal	Normal	
Abnormal (probable DLB)	True Positive (TP)	False Negative (FN)	TP + FN
Normal (non-DLB)	False Positive (FP)	True Negative (TN)	FP + TN
Column Total	TP + FP	FN + TN	N

Sensitivity and specificity (with DaTSCAN SPECT visual assessments and Consensus Panel clinical diagnosis) were defined as follows:

Sensitivity=TP/(TP+FN) i.e. the percentage of times that the image diagnosis was DLB given that the clinical diagnosis was DLB.

Specificity=TN/(TN+FP) i.e. the percentage of times that the image diagnosis was non-DLB given that the clinical diagnosis was non-DLB.

Secondary efficacy endpoints

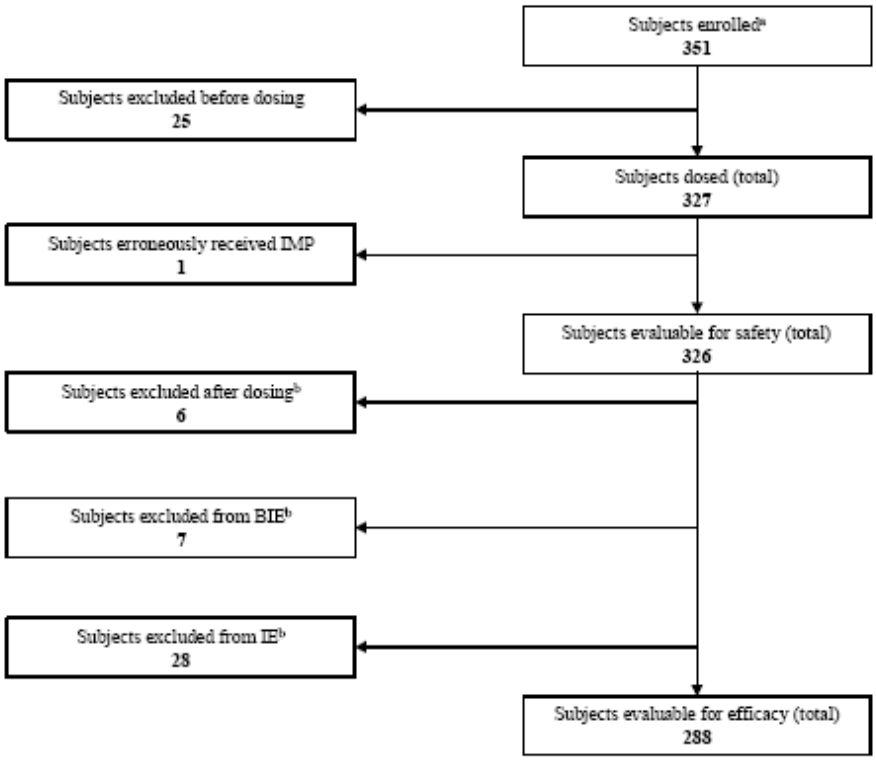
1. Accuracy =(TP+TN)/(TP+FP+TN+FN) i.e. the percentage of times the image diagnosis matched the clinical diagnosis,
   Positive Predictive Value (PPV)=TP/(TP+FP) i.e. the percentage of times that the clinical diagnosis was DLB given that the image diagnosis was DLB
   Negative Predictive Value (NPV)=TN/(TN+FN) i.e. the percentage of times that the clinical diagnosis was non-DLB given that the image diagnosis was non-DLB
2. Semi-quantitative analysis (ROI) of the DaTSCAN images to compare striatal uptake ratios of DaTSCAN between the 3 groups of probable, possible and non-DLB in specific regions of interest (i.e., striatum, caudate, and putamen in both hemispheres)
3. Assessment of the impact of DaTSCAN SPECT visual assessment findings on the on-site investigator's ability to establish a diagnosis, to make management decisions and thereof on the confidence of diagnosis by comparing pre- and post-imaging results
4. Summary of the proportions of abnormal DaTSCAN SPECT visual assessment findings in relation to the groups of probable DLB, possible DLB, and non-DLB as established by an independent CP

Statistical Analyses

For both diagnostic parameters, an exact 1-sided binomial test was used to test the null hypothesis H_0: $p \leq p0$. In this case, p0 represented a pre-defined threshold for sensitivity or specificity. The alternate hypothesis was given by H_1: $p > p0$. The parameter p represented the sensitivity or specificity for an independent blinded reader's diagnosis with access to DaTSCAN SPECT imaging. The thresholds (p0) for sensitivity and specificity under the null hypothesis were respectively 0.65 and 0.73. Each test was conducted at the 0.025 significance level.

Results

A total of 351 patients were enrolled into this study and the *patient disposition* is given in the figure below.



A total of 25 subjects were excluded prior to dosing; of these patients 14 had a clinical diagnosis (10 non-DLB, 3 probable DLB, and 1 possible DLB). Although there is an imbalance between clinical diagnoses, with only 14 patients for which a clinical diagnoses are available, it is unlikely that these would alter the conclusions from this study.

Efficacy results were based on the performance of 3 blinded image readers relative to the CP diagnosis.

- Results of the CP assessment (surrogate "standard of truth")

All cognitive, neuropsychiatric, neurological, clinical, and laboratory data including the on-site investigator's clinical diagnosis and recommended subject management decision (non-pharmacological measures, ChE inhibitors, parkinsonian agents, neuroleptic agents, or other) before DaTSCAN SPECT imaging along with the level of confidence thereof, as well as any available MRI, CT, or cerebral perfusion SPECT findings (if performed) were provided to the CP. *Post-mortem* data that became available during the study were also provided. The CP was not provided with the subject's DaTSCAN SPECT image results or with the on-site investigator's post-imaging diagnosis or management decisions.

Table 14 CP Assessment

N	Standard of Truth: Clinical Diagnosis by the CP													
	DLB				Non-DLB									
	Probable DLB		Possible DLB[b]		Probable AD		Possible AD		Probable VaD		Possible VaD		Other[a]	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
288	88	30.6	56	19.4	90	31.3	34	11.8	1	0.3	8	2.8	11	3.8

N = Efficacy population; n = Number of subjects with respective diagnosis.
[a] = "Other" diagnoses are specified in Listing 16.2.6.2.1.
[b] = Subjects with a diagnosis of "possible" DLB are not included in the confirmatory analysis.
REF: Section 14.2, Table 14.2.2.1

The 56 subjects with "possible DLB" were not included in the analysis of the primary efficacy endpoint or in the analysis of secondary endpoints 1 and 3. *Post-hoc* analyses including these patients were requested by CHMP. The 11 subjects with a diagnosis of "other" were verified as having dementia (i.e., the criteria were met according to on-site investigator's entries into the CRF). In all cases the diagnosis was set to "non-DLB" for the statistical analysis. Twenty eight subjects could not be included in the efficacy population because a diagnosis of either probable DLB, possible DLB, or non-DLB could not be established by the CP based on the clinical data available or due to violation of study entry criteria. Without a definite CP diagnosis as the standard of truth the subjects could not be included in the statistical analysis of all planned endpoints.

In addition, the CP was asked to state whether concomitant cerebral disease was present. According to the CP this was the case in 19 (6.6%) of the 288 subjects included in the efficacy population. The majority of these subjects (N = 11, 57.9%) was diagnosed by the CP as having "possible VaD" in addition to their main diagnosis. Five subjects (26.3%) had "possible AD".

- Results of the DaTSCAN independent blinded image evaluation (BIE)

The following figure shows the disposition of the efficacy population

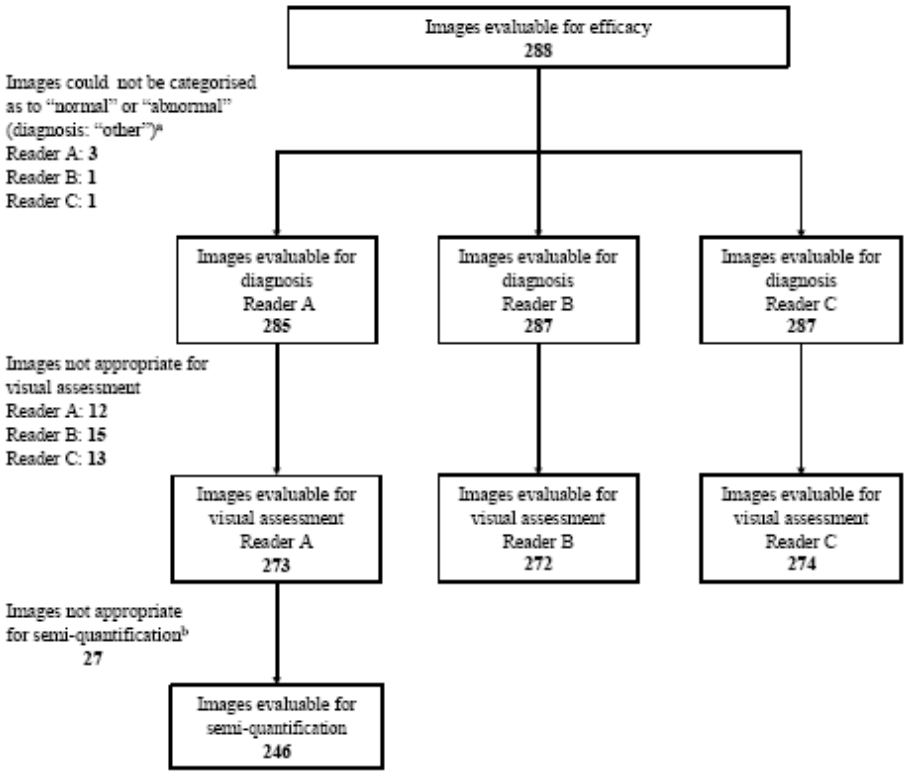


Table 19 Independent BIE of DaTSCAN SPECT Images

SPECT Reader	N	Visual Assessment of Images									
		Normal		Abnormal Type 1		Abnormal Type 2		Abnormal Type 3		Other[a]	
		n	%	n	%	n	%	n	%	n	%
A	273	172	63.0	11	4.0	70	25.6	16	5.9	4	1.5
B	272	174	64.0	19	7.0	41	15.1	34	12.5	4	1.5
C	274	176	64.2	11	4.0	62	22.6	23	8.4	2	0.7

N = number of subjects with evaluable images for that reader.
[a] = "Other" assessments are specified in Listing 16.2.6.3.1.
REF: Section 14.2, Table 14.2.3.3

A total of 5 patients were classified as having either "unevaluable" or "other" images and no clinical diagnosis. Including these patients in a sensitivity analysis is unlikely to alter the conclusions from this study.

Analysis of the co-primary efficacy endpoint

A total of 232 subjects with a diagnosis of either "probable" or "non-DLB" were included in the analysis. Subjects with a diagnosis of "possible" DLB were excluded.

Table 20 Sensitivity and Specificity of DaTSCAN SPECT Imaging in Differentiating Between Probable DLB and Non-DLB Subjects – Comparison of Readers

Parameter	Reader	N	n	%-Value	eLCL	eUCL	p (1-sided)
Sensitivity	A	81	63	77.8	67.2	86.3	0.009*
	B	80	60	75.0	64.1	84.0	0.037
	C	81	65	80.2	69.9	88.3	0.002*
Specificity	A	139	127	91.4	85.4	95.5	<0.001*
	B	140	124	88.6	82.1	93.3	<0.001*
	C	138	126	91.3	85.3	95.4	<0.001*

N = Number of subjects with non-missing values for parameter; n = Number of subjects with positive values (success); LCL = lower confidence limit; UCL = upper confidence limit; e = exact (95%; 2-sided);
p = p-value (exact 1-sided binomial test versus a threshold value of 65% for sensitivity and 73% for specificity).
* = p-value of <0.025 (statistically significant).
REF: Section 16.1.9.2, Table 16.1.9.2.1.1, 16.1.9.2.1.3

The sensitivity ranged between 75.0% and 80.2%. The pre-defined threshold value for sensitivity was 65%. The LCL was below (by 0.9%) the threshold value for reader B (64.1). The specificity was between 88.6% and 91.4%. The pre-defined threshold value for specificity was 73%.

According to the study protocol, the projected achievable sensitivity and specificity values were 80% and 85%, respectively. For sensitivity, the expected rate was reached by reader C and was lower for the other 2 readers (by 2.2% and 5%). For specificity, the expected rate was exceeded by all 3 readers (by 3.6% to 6.4%).

In addition, an intention-to-diagnose (ITD) analysis was performed, which included subjects with non-evaluable images not related to DaTSCAN. Since all additional subjects had to be treated as mismatches to the CP diagnosis, this analysis resulted in a decrease of sensitivity (between 63.8% and 69.1%) and specificity (between 84.9% and 87.0%), although the results remain acceptable.

Thus, the study results show that DaTSCAN can differentiate DLB from AD (Alzheimer's disease). Given that patients with PDD were excluded and only 9 patients with VaD (Vascular Dementia) were included, it is not possible to extend the results to "other forms of dementia" as claimed by the Applicant. This is reflected in the indication proposed by CHMP.

Analysis of secondary efficacy endpoints

- *endpoint 1*

Table 21 Accuracy, PPV and NPV of DaTSCAN SPECT Imaging in Differentiating between Probable DLB and Non-DLB Subjects – Comparison of Readers

Parameter	Reader	N	n	%-Value	eLCL	eUCL
Accuracy	A	220	190	86.4	81.1	90.6
	B	220	184	83.6	78.1	88.3
	C	219	191	87.2	82.1	91.3
PPV	A	75	63	84.0	73.7	91.4
	B	76	60	78.9	68.1	87.5
	C	77	65	84.4	74.4	91.7
NPV	A	145	127	87.6	81.1	92.5
	B	144	124	86.1	79.4	91.3
	C	142	126	88.7	82.3	93.4

N = Number of subjects with non-missing values for parameter; n = Number of subjects with positive values (success); LCL = Lower Confidence Limit; UCL = Upper Confidence Limit;
e = exact (95%).
REF: Section 16.1.9.2, Table 16.1.9.2.1.1

The results are acceptable and there is a good reliability between the 3 readers.

- *endpoint 2*- A total of 69 subjects with probable DLB, 48 subjects with possible DLB, and 129 subjects with non-DLB were evaluable for the semi-quantitative assessment.

Table 22 Summary of DaTSCAN Specific Uptake Ratios in Subjects with Probable (N=69), Possible (N=48) or Non-DLB (N=129) as Established by the CP

Region	Classification	Mean	SD	Min	Max
Striatum Right	Probable DLB	1.1	0.65	0.3	2.9
	Possible DLB	1.7	0.73	0.6	3.2
	Non-DLB	2.2	0.55	0.6	3.9
Striatum Left	Probable DLB	1.1	0.63	0.4	2.7
	Possible DLB	1.7	0.74	0.6	3.2
	Non-DLB	2.2	0.56	0.6	3.8
Putamen Right	Probable DLB	0.9	0.68	0.1	2.7
	Possible DLB	1.5	0.73	0.3	3.0
	Non-DLB	2.0	0.56	0.3	3.7
Putamen Left	Probable DLB	0.9	0.75	0.3	2.8
	Possible DLB	1.5	0.55	0.3	3.0
	Non-DLB	2.0	0.61	0.3	3.6
Caudate Right	Probable DLB	1.3	0.61	0.3	3.0
	Possible DLB	1.9	0.73	0.7	3.5
	Non-DLB	2.3	0.55	0.9	3.8
Caudate Left	Probable DLB	1.3	0.59	0.4	2.8
	Possible DLB	1.8	0.70	0.7	3.3
	Non-DLB	2.2	0.58	0.8	3.8

SD = Standard Deviation; Min = Minimum; Max = Maximum
REF: Section 16.1.9.2, Table 16.1.9.2.2.1

A markedly greater loss in the density of the presynaptic dopamine transporter protein (DaT), which is said to be diagnostic for DLB, should be reflected by a corresponding decrease in DaTSCAN radio uptake. For each of the 3 regions and in each hemisphere there was a reduction in uptake ratio in the probable DLB compared to the non-DLB population. Subjects classified as "possible" DLB by the CP showed intermediate reductions in uptake and a bimodal distribution. This bimodal distribution could be due to the fact that some "possible" DLB may be classified as "probable" DLB and the other "possible" DLB as non-DLB (i.e. AD).

- endpoint 3 - The ability of DaTSCAN to increase the investigator's diagnostic performance was assessed by comparing the investigator's baseline diagnosis to the post-DaTSCAN diagnosis.

Table 23 Comparison of On-site Clinical Diagnosis Pre- and Post-DaTSCAN Imaging to CP Diagnosis

Parameter	N	Pre-DaTSCAN		Post-DaTSCAN		p
		n	%	n	%	
Sensitivity	88	87	98.9	78	88.6	0.004
Specificity	143	132	92.3	132	92.3	1.000
Accuracy	231	219	94.8	210	90.9	0.049

N = Number of subjects with non-missing values for on-site clinical diagnosis pre- and post-DaTSCAN; n = Number of subjects with positive values (success) for that variable; p = p-value for McNemar's test (exact, 2-sided)
REF: Section 16.1.9.2, Table 16.1.9.2.3.1

- endpoint 4-

Table 26 Proportion of Abnormal DaTSCAN SPECT Visual Assessment Findings in Relation to the Groups of Possible, Probable DLB, and Non-DLB as Established by an Independent CP

DaTSCAN SPECT Reader	CP Diagnosis	N	n	Proportion (%)	eLCL	eUCL	p
A	Probable DLB	81	63	77.8	67.2	86.3	<0.001
	Possible DLB	53	22	41.5	28.1	55.9	nap
	Non-DLB	139	12	8.6	4.5	14.6	<0.001
B	Probable DLB	80	60	75.0	64.1	84.0	<0.001
	Possible DLB	52	20	38.5	25.3	53.0	nap
	Non-DLB	140	16	11.4	6.7	17.9	<0.001
C	Probable DLB	81	65	80.2	69.9	88.3	<0.001
	Possible DLB	55	19	34.5	22.2	48.6	nap
	Non-DLB	138	12	8.7	4.6	14.7	<0.001

N = Number of subjects with non-missing values for DaTSCAN SPECT visual assessment; n = Number of subjects abnormal DaTSCAN SPECT visual assessment findings; Proportion = n/N*100 ; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit; e = exact (95%); p = p-value (Fisher's exact test, 2-sided; the proportion of abnormal DaTSCAN SPECT visual assessment findings in the group of probable DLB and non-DLB were compared to the group of possible DLB); nap = not applicable.
REF: Section 16.1.9.2, Table 16.1.9.2.4

Further to a Request from CHMP for additional sensitivity analyses for sensitivity, specificity, PPV and NPV, the MAH performed 2 additional analyses where the 56 patients diagnosed with "possible DLB" were all assumed to have a clinical diagnosis of DLB and an analysis in which they were assumed to be diagnosed as non-DLB. When the "possible DLB" patients were included as DLB patients, the sensitivity ranged from 60.6-63.4% and specificity from 88.6-91.4%. When the "possible DLB" patients were included as non-DLB patients, the sensitivity ranged from 75-80.2% and specificity from 81.3-83.9%. Patients with undeterminable clinical diagnosis or unevaluable/other images were then included by assuming that they were 'false' diagnoses. For this analysis the sensitivity ranged from 46.5% - 49.7% and specificity from 81.6% - 84.1% when patients diagnosed with "possible DLB" were assumed to have DLB. The sensitivity ranged from 52.2% - 57.5% and specificity from 74.6% - 77.1% when patients diagnosed with possible DLB were assumed to have non-DLB.

Although these sensitivity analyses show that the results are not particularly robust to missing data, the MAH included two less conservative sensitivity analyses in which "possible DLB" patients were not included. In one of these analyses all subjects with images unevaluable were considered to be 'false' results (ITD) and in the other analysis the on-site diagnosis was considered to be the standard of truth in subjects whose Consensus Panel diagnosis was missing. For the ITD analysis the sensitivity ranged from 63.8% to 69.1% and specificity from 84.9% - 87%; and for the on-site diagnosis the sensitivity ranged from 74.1% to 79.1% and specificity from 89.5% to 92.1%.

Given these sensitivity analyses it may be considered that the best use of DaTSCAN would be in those patients with a "probable" diagnosis of DLB. The results of the sensitivity analyses that included "possible DLB" patients have been included in section 5.1 of the SPC

Additional efficacy analyses

Inter-reader and intra-reader agreements

Table 27 Inter-Reader Agreement between each Pair of On-site and Independent SPECT Readers in Visual Assessment of DaTSCAN SPECT Images (Abnormal/Normal)

Reader Pair	N	Cohen's κ	LCL	UCL
Reader A Reader B	264	0.82	0.75	0.90
Reader A Reader C	262	0.91	0.85	0.96
Reader B Reader C	259	0.85	0.78	0.91
Reader A, B, C[a]	254	0.87	0.79	0.94
Reader A On-Site	273	0.67	0.58	0.75
Reader B On-Site	272	0.59	0.50	0.68
Reader C On-Site	274	0.63	0.54	0.72

N = Number of images with non-missing value for DaTSCAN SPECT visual assessment for the 2 respective readers; for the generalised kappa: number of images with non-missing values for all 3 readers; LCL = Lower Confidence Limit; UCL = Upper Confidence Limit (95%);
A, B, C = Independent SPECT readers.
[a] Multiple coefficient for all 3 independent SPECT readers.
REF: Section 16.1.9.2, Table 16.1.9.2.5.1

On-site clinical diagnosis

The on-site clinical diagnosis was established by the investigator before and after the DaTSCAN imaging. This diagnosis was based on all available cognitive, neuropsychiatric, neurological, and clinical data. After the baseline testing was completed, the investigator was asked to establish the diagnosis as to probable DLB, possible DLB, or other forms of dementia (e.g., AD, VaD) using internationally accepted diagnostic criteria (including the ICC). The on-site investigators were then asked for a final clinical diagnosis to be made on the basis of all available subject information – including DaTSCAN image findings.

Table 15 On-Site Clinical Diagnosis at Baseline (Pre-DaTSCAN)

CP Diagnosis	N	On-site Clinical Diagnosis									
		Probable DLB		Possible DLB		AD		VaD		Other Diagnosis[a]	
		n	%	n	%	n	%	n	%	n	%
Total	288	106	36.8	40	13.9	130	45.1	9	3.1	3	1.0
Probable DLB	88	79	89.8	8	9.1	1	1.1	0	0	0	0
Possible DLB	56	23	41.1	25	44.6	6	10.7	1	1.8	1	1.8
Non-DLB	144	4	2.8	7	4.9	123	85.4	8	5.6	2	1.4

N = Efficacy population for respective analysis; n = Number of subjects with respective diagnosis.
a = "Other" diagnoses are specified in Listing 16.2.6.1.1.
REF: Section 14.2, Table 14.2.1.1.1

Table 16 On-Site Clinical Diagnosis after DaTSCAN Imaging

CP Diagnosis	n	On-site Clinical Diagnosis			
		Non-DLB		DLB	
		n	%	n	%
Total	288	158	54.9	130	45.1
Probable DLB	88	10	11.4	78	88.6
Possible DLB	56	15	26.8	41	73.2
Non-DLB	144	133	92.4	11	7.6

N = Efficacy population for respective analysis; n = Number of subjects with respective diagnosis.
REF: Section 14.2, Table 14.2.1.1.4

The on-site clinical diagnosis at baseline was in agreement with the CP diagnosis in 89.8% of the cases for "probable" DLB, 44.6% of the cases for "possible" DLB and 92.4% of the cases for non-DLB.

Comparison of Results in Subpopulations in PDT301

Analyses for sensitivity, specificity, and accuracy were performed for the following subgroups: age, presence of parkinsonism (as justified by UPDRS), severe dementia/cognitive impairment, (as justified by MMSE), study centre, and dose of radioactivity administered.

The results show a lower sensitivity (approximately 60% compared to the CP 85%) for the age groups <65 years and >80 years, but the number of patients in each subgroup (7 subjects < 65 years and 14 subjects > 80) are too small to draw any meaningful conclusion. there was no significant difference in sensitivity or specificity between injected activities related to doses > or < 185 MBq for each of 3 Readers, although sensitivity and specificity values were slightly higher when the administered activity is >185 MBq,

3.3.2 Clinical safety

Patient exposure

The safety review submitted by the MAH includes 3 studies with 529 patients: 2 proof-of-concept studies (Middlesex Study & Newcastle study) and 1 phase III study (PDT301 study). All patients included in these studies received a single intravenous injection of DaTSCAN at the following doses:

Study	N° of subjects	Dose range
Proof of concept studies	244	150 to 185 MBq
Pivotal Phase III trial (PDT 301)	326	121 to 287 MBq
Overall dose range	570	121 to 287 MBq

Death and Discontinuation due to adverse events (AEs)

One subject was withdrawn in study PDT301 after receiving DaTSCAN because of the occurrence of a SAE (fractured neck of femur), which resulted in the subject's death. This AE was considered as not related to DaTSCAN by the investigator.

Adverse events including serious adverse events

A total of 44 subjects experienced at least one *AEs* and 2 patients experienced a serious AE:

- 1 subject in the Middlesex study experienced incontinence and 1 subject in the Newcastle study experienced neck pain. Both AEs were considered as unrelated to DaTSCAN.
- 42 subjects among the 326 subjects included in the study PDT301 experienced a total of 51 AE. Two subjects experienced a SAE (pyrexia and the above death secondary to femoral neck fracture) and both were considered related to the subject's medical condition and unrelated to DaTSCAN . . The AEs reported in more than 1 patient were: injection site haemorrhage (n=12), injection site erythema (n=9), nausea (n=5) and back pain (n=2). Ten out of the 51 AE were considered as related: 3 cases of nausea, 2 cases of injection site haemorrhage, 2 cases of injection site erythema, 1 case of dry mouth, 1 case of vomiting and 1 case of headache. The other AE were considered as unrelated to DaTSCAN but related to procedural complication or to other cause.

The observed AE were of transient nature, considered as expected for this disease and the age of patients.

Others

Assessment of laboratory parameters (haematology, serum biochemistry, urinalyses), vital signs and ECGs revealed no trends or signals indicative of a safety signal.

Post-marketing safety data

A total of 5 non-serious cases were reported during the period 27 July 2000 – 31 January 2004 (4 injection site pain and 1 case including dysgueusia immediately, headache, nausea and anxiety 3 hours after DaTSCAN injection). Events resolved. In the study PDT 304, a total of 202 patients were enrolled and no serious AE were reported.

III. DISCUSSION

The documentation submitted by the Applicant contains efficacy data obtained from 2 investigator-sponsored studies and 1 pivotal phase 3 study. The two investigator studies (the Middlesex study and the Newcastle study) are limited because of the non-independent analysis of results, the absence of specified inclusion and exclusion criteria and test hypothesis, and the unblinded image analysis of one of the experts. These two studies, which include autopsy findings, can be considered as proof-of-concept for DaTSCAN imaging, as claimed by the MAH.

The "standard of truth" in all 3 studies was the clinical diagnosis of DLB. The main pivotal study was designed to assess the diagnostic accuracy of DaTSCAN images versus clinical diagnosis. Both the clinical diagnoses of the "standard of truth" and the DaTSCAN image reading were carried out independently of each other, thus reducing the chance of artificially increasing the sensitivity and specificity of the results. The results for the primary endpoints (sensitivity and specificity) and main secondary endpoints (positive predictive value, negative predictive and accuracy) are considered acceptable and are included in section 5.1 of the SPC.

One of the issues discussed by CHMP was whether clinical diagnosis is of sufficient standard to be considered a *"very good approximation to the true disease state" (*as suggested in the CHMP *Points to Consider on diagnostic agents* CPMP/EWP/1119/98*),* especially given the findings of the Middlesex study, where the specificity for clinical diagnoses was only 30% when compared with autopsy data (considered the "gold standard"). Indeed, it was suggested during the evaluation that, in absence of the autopsy data, the best reference might have been clinical follow-up of patients (e.g. 12 months or longer) with an uncertain diagnosis in the beginning. However, the MAH argued that the Consensus Panel approach had been validated and actually agreed with some national Regulatory Agencies. Furthermore, the MAH claim that using 12-month follow up data to confirm the initial diagnosis would not add significant value as it becomes more difficult to distinguish subtypes as dementia progresses, a view supported by published literature (Ballard et al). Moreover, the collection of *post-mortem* data would not be practical due to the low incidence of mortality in this population. The CHMP accept these arguments but nonetheless wish to receive the data arising from the re-evaluation of the primary and secondary endpoints at 12 months and any *post-mortem* information that becomes available from study PDT301, as a post-approval commitment.

Regarding the limited accuracy of clinical diagnosis observed in the Middlesex study, the Applicant has explained that since the study recruitment period predated the ICC, it relied solely upon the clinical diagnosis of a single investigator and did not adopt the Consensus Panel approach used both in the Newcastle studies and in the pivotal study PDT301. This 3-way consensus method has previously been shown to have high validity against neuropathological diagnosis. In light of the CP approach, the reliance on a single clinician to establish diagnosis was a methodological weakness in the Middlesex study, which resulted in suboptimal diagnostic accuracy. Indeed this weakness in the Middlesex study illustrates the need for a consensus panel approach if the clinical diagnosis is to be used as a standard of truth, and illustrates the need for a biomarker such as DaTSCAN to improve diagnostic precision, given that diagnosis established by a CP of international experts in the field of dementia does not reflect the real life clinical setting. The real importance of the Middlesex study was in providing longitudinal post-mortem data demonstrating a high correlation between abnormal DaTSCAN image findings and a neuropathological diagnosis of LBD. The ongoing analysis of these data (17 cases to date) has demonstrated the sensitivity of DaTSCAN SPECT imaging to be 100% with semi-quantitative analysis and 86% with the visual assessment and the specificity to be 90% and 80%, respectively.

Another point extensively debated by the Committee was whether the Applicant had chosen the most appropriate subpopulation of DLB patients for the main efficacy analyses, given that the diagnostic uncertainty in "probable" DLB patients is low, whereas subjects with "possible DLB", whose diagnostic uncertainty is higher and would, *a priori*, derive a greater benefit from the use of DaTSCAN, were excluded from the analyses. *Post-hoc* sensitivity analyses including "possible" DLB patients submitted by the Applicant at the request of CHMP show a decrease in the values for the main efficacy endpoints and have been reflected in section 5.1 of the SPC. While the MAH appreciates that the greatest utility of DaTSCAN imaging would be in those patients with clinical uncertainty, they claim that the diagnosis of DLB based solely on clinical criteria remains difficult and is to some degree uncertain, even in patients with probable DLB, as reflected in recent publications. Study PDT301 was designed to demonstrate the efficacy of DaTSCAN within the confines of uncertainty defined by a clinical diagnosis of "probable DLB" as diagnosed by the CP. Here, the standard of truth had to be validated and as accurate as possible. The inclusion of patients meeting clinical criteria for "possible" DLB enabled the evaluation of DaTSCAN in a population in whom the degree of certainty of the clinical diagnosis based on validated clinical criteria (i.e., the ICC) is low (accuracy of approximately 50% or less). The Applicant also states that the inclusion of "possible" DLB patients into the primary endpoint analysis would thus have had a misleading effect on the primary efficacy parameters and as such these subjects were excluded from the efficacy analyses..

While the CHMP acknowledges the arguments put forward by the Applicant, in view of these sensitivity analyses it may be considered that the best use of DaTSCAN would be in those patients with a "probable" diagnosis of DLB, which also more adequately reflects the trial results. This has been reflected in the approved indication and the results of the sensitivity analyses including "possible DLB" patients have been included in section 5.1 of the SPC.

The third main point discussed by CHMP refers to the *clinical utility* of DaTSCAN as a diagnostic test for LBD given that the clinical consequences of accurate and earlier diagnosis would appear limited in terms of patient prognosis and disease management. Indeed, during the evaluation it was put to the Applicant whether the DaTSCAN does not merely confirm what is already clinically known, namely that patients diagnosed as DLB already have parkinsonism as this is a core feature of the diagnosis, and hence a decreased uptake of dopamine is expected. The Applicant argues that the presence of parkinsonism is not only related to DLB. Up to 25% of AD patients can also develop levodopa-resistant parkinsonism not related to the dopaminergic neurons. At autopsy, such patients demonstrate an accumulation of neuro-tangles in the basal ganglia rather than the dopaminergic degeneration characteristic of synucleopathies such as DLB [Ballard et al. 2004, Ceravolo et al. 2004]. Thus, parkinsonism can be absent in a DLB patient and can also be present in a subject with a neuropathological diagnosis of AD, making DAT scanning particularly useful in distinguishing between the two disorders, as explained by McKeith *et al*. Hence DaTSCAN can be of particular value in detecting the presence or absence of nigrostriatal involvement in these populations and thus dictating future patient management, which can differ as detailed in the introduction to this report.

To conclude, the study results show that DaTSCAN can differentiate DLB from AD (Alzheimer's disease). Given that patients with PDD were excluded and only 9 patients with VaD (Vascular Dementia) were included, it is not possible to extend the results to "other forms of dementia" as claimed by the Applicant. In addition, in view of the sensitivity analyses including patients with "possible DLB", it may be considered that the best use of DaTSCAN would be in those patients with a "probable" diagnosis of DLB, which also more adequately reflects the trial results. Thus, a revised, more restricted indication reflecting the main study population and results has been approved by CHMP.

The CHMP considers that DaTSCAN is a useful diagnostic agent that will help to improve the accuracy of the diagnosis of DLB, which appears to vary substantially from study to study, in the real life clinical setting and there is little apparent risk associated with its use.

IV. CONCLUSION

On 28 June 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet

The Follow-Up Measure below has been agreed:

Area[1]	**Description**	**Due date**[2]
Clinical	Protocol -PDT301 Study Title- An Open-label, Phase 3, Clinical Study to Assess the Striatal Uptake of an Intravenous Solution Containing the Dopamine Transporter Radio-ligand, DaTSCAN, in Subjects with Dementia with Lewy Bodies. Brief Description –To determine the diagnostic efficacy (i.e. sensitivity and specificity) of the visual assessment of DaTSCAN single-photon emission computed tomography (SPECT) images in differentiating between probable dementia with Lewy Bodies (DLB) and non-DLB subjects as determined by the clinical diagnosis of an independent consensus panel used as the standard of truth, and to examine the safety profile of a single intravenous injection of DaTSCAN. Data to be submitted – Data arising from re-evaluation of the primary and secondary endpoints at 12 months including any post-mortem data that is available.	Q1 2007