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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD. Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

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Keywords: Parkinson's disease, Movement disorders, Dementia, SPECT, Neuroradiology

Primary Subject Heading: Neurology

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Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging indeed has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.

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- Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis used is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. Numerous clinical trials have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[3, 13-18] However, each trial had limited numbers of subjects for whom results were available, ranging from 20 to 326.[3, 16] To better estimate the diagnostic performance of ioflupane (^{123}I), we conducted a pooled analysis. Four clinical trials (three Phase 3 and one Phase 4) performed to support the US New Drug Application (NDA) were chosen for this pooled analysis because of their similar designs, methodologies, endpoints, and patient populations. It should be noted that this is a pooled analysis, and is not a meta-analysis of peer-reviewed publications.

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METHODS

Participants

Four clinical trials were used for this pooled analysis, based on their similar designs and objectives; we used source data from studies performed in support of the ioflupane (^{123}I) US NDA.[3, 13-15, 17] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN™ or DaTscan™ , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[19] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. PDT03004 is also known as PDT304, and will be referred to as PDT304 throughout this paper. Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[3, 13-15, 17] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection.

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Ioflupane (^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images.

Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all

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dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

This pooled analysis of four clinical trials provides the largest set of clinical evidence to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, ioflupane (^{123}I) SPECT image evaluation demonstrated a sensitivity (ability to detect an SDDD when it is present) ranging from 75.0% to 96.5%, and a specificity (ability to exclude an SDDD when it is absent) ranging from 83.0% to 100.0%. Inter-reader agreement was high, indicating that diagnostic accuracy is not dependent upon individual expert performance.

When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 15, 20] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies (PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003,

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enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[16, 19] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[16] Therefore, the use of clinical diagnosis as the non-perfect reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy,

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with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[21] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[22] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[22] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[23] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I) imaging results became available.[6, 24] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[25, 26] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[25] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

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Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[27] The Society of Nuclear Medicine,[28] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[29] the Scottish Intercollegiate Guidelines Network (SIGN),[30] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[31] Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[18, 32, 33] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[34] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA, DLB) and tauopathies (PSP, corticobasal degeneration).[35, 36]

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Literature Review and Interpretation

We searched PubMed on October 4, 2013 using the terms (*FP-CIT or *Ioflupane[Title]) AND (Lewy or dementia or parkinson* or essential tremor[Title]) AND (diagnos* or accura*[Title]) and applied the filter "Human." The search retrieved 181 articles. After reviews, case reports, and commentaries were removed, 138 remained. Of these, 28 were clinical studies that evaluated the diagnostic accuracy of ioflupane (^{123}I),[3, 13-17, 37-59] with the number of subjects ranging from 16[53] to 326.[14] We selected four of these, which were the studies that supported the US NDA. We also found in our search a meta-analysis[60] of the diagnostic accuracy of ioflupane (^{123}I) in DLB was performed in 2012 and summarized four studies with a total of 419 subjects. One of the studies included in this meta-analysis is the PDT301 study (with the baseline clinical evaluation)[3] included in our pooled analysis.

This pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date of the diagnostic accuracy of ioflupane (^{123}I) SPECT imaging. The analysis includes patients with dementia and/or movement disorders. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75·0% to 96·5%, and specificity ranged from 83·0% to 100·0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0·81 to 1·00. Adoption and utilization of this new technology is expanding, reinforcing the usefulness of ioflupane (^{123}I) imaging as a validated diagnostic tool.

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Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies).

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

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WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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GE Healthcare provided funding and administrative support for this pooled analysis; managed statistical analysis, medical writing, and interpretation of the data; drafted sections of the manuscript; and reviewed, edited, and approved the manuscript.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

Dr. O'Brien reports grants and other from GE Healthcare, grants and other from Lilly, other from Bayer Healthcare, other from TauRx, other from Cytox, outside the submitted work.

Dr. Oertel reports grants and personal fees from GE Healthcare, personal fees from Amersham.Buchler, outside the submitted work.

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Dr. Walker reports personal fees from GE Healthcare, personal fees from Bayer Healthcare, grants from GE Healthcare, grants from Lundbeck, other from GE Healthcare, and personal fees from Novartis, outside the submitted work.

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Dr. Sherwin reports other (salary) from GE Healthcare, during the conduct of the study; other (salary) from GE Healthcare, outside the submitted work.

Dr. Grachev reports employment from GE Healthcare, during the conduct of the study.

Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

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Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

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DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies).

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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Dr. Tatsch reports grants and personal fees from GE Healthcare, outside the submitted work.

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Dr. Sherwin reports other (salary) from GE Healthcare, during the conduct of the study; other (salary) from GE Healthcare, outside the submitted work.

Dr. Grachev reports employment from GE Healthcare, during the conduct of the study.

Data Sharing Statement

Informed consent was not obtained from study participants for data sharing, but the presented data are anonymized and risk of identification is low. No additional data are available.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

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3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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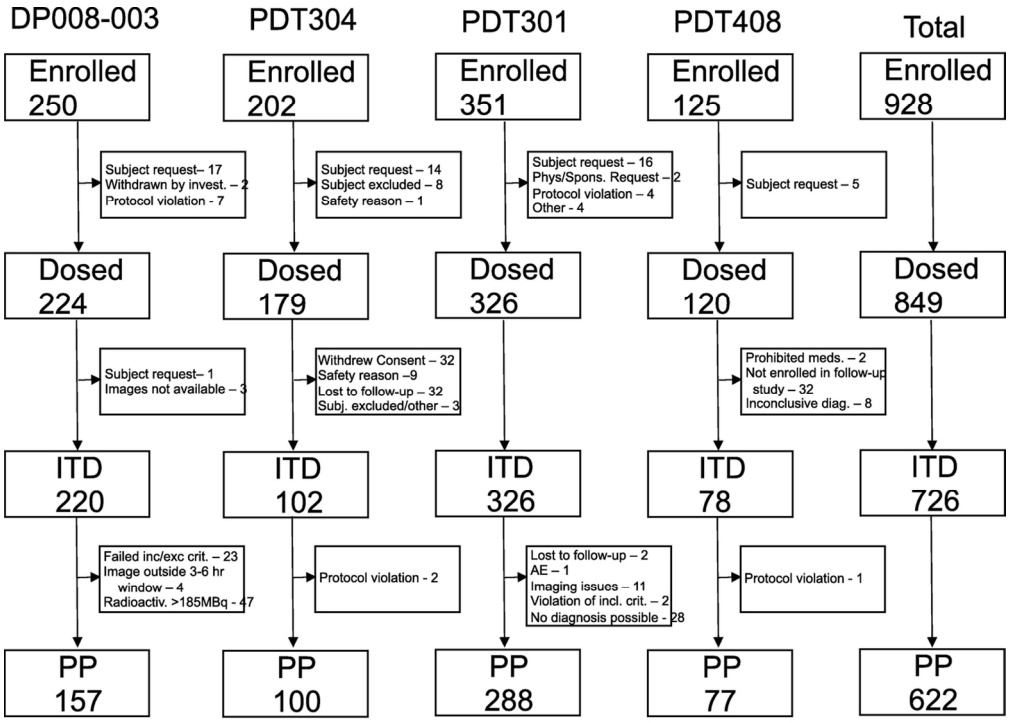

Note: Subjects may have more than one reason for discontinuing.

Figure 1. Subject disposition
124x95mm (300 x 300 DPI)

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Fig. 2a

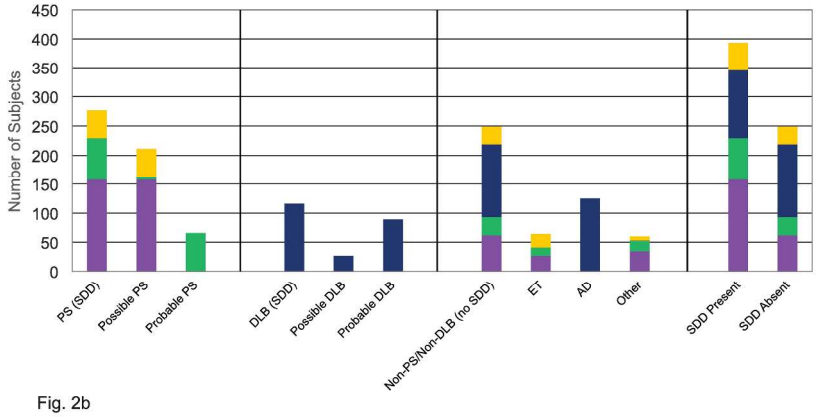

Fig. 2b

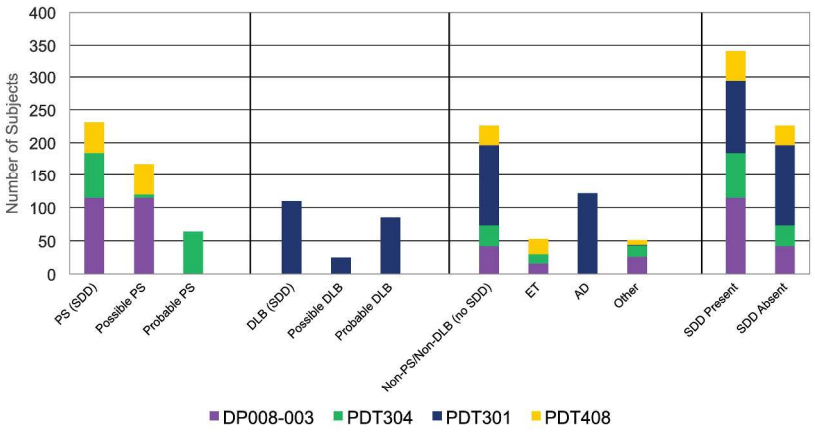

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study
Fig 2a. – ITD population
Fig 2b. – PP population
332x391mm (300 x 300 DPI)

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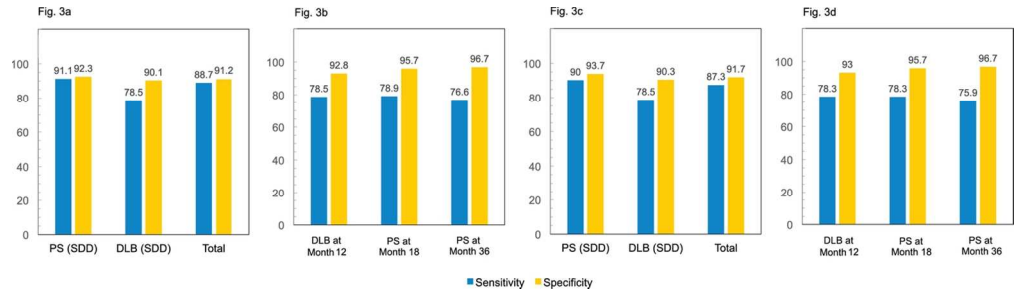

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDD present vs. SDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDD present vs. SDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

123x34mm (300 x 300 DPI)

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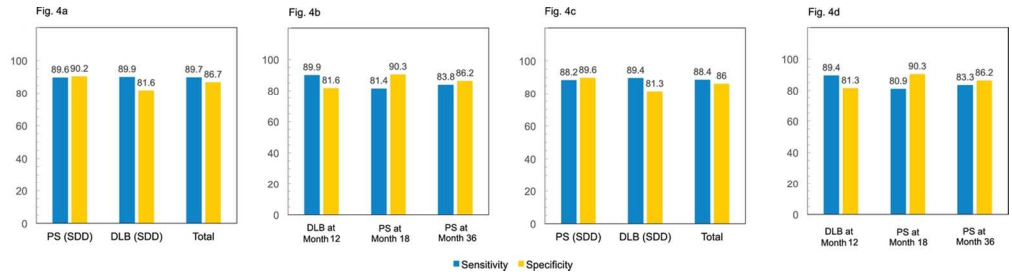

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDD present vs. SDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDD present vs. SDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

121x32mm (300 x 300 DPI)

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Table S1. Investigators who participated in the four clinical trials in this pooled analysis.

DP008-003

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PDT408	
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Table S2. Ethics Committees for the Four Studies in the Pooled Analysis

Study DP008-003

Committee Name	City	Country	Chairman
Medical Research Ethics Committee, The Phillips University Clinic	Marburg	Germany	Dr. P Heubel
The Faculty of Medicine Ethics Committee, Ludwig Maximilian University of Munich	Munich	Germany	Prof. Dr. med. Dent. W Gernet
Southern General Hospital Medical Ethics Committee	Glasgow	UK	Rev. D Keddie
Medical Ethics Committee, Academic Medical Center, Amsterdam University	Amsterdam	The Netherlands	Prof. L Arisz
Joint UCL/UCLH Committees on the Ethics of Human Research	London	UK	Prof. A McLean
Ethics Review Committee, University Hospital	Ghent	Belgium	Prof. Dr. M Bogaert

PDT301

Committee Name	City	Country	Chairman
Ethikkommission des Landes Oberösterreich	Linz	Austria	Univ. Prof. Prim Dr. Fisher
Ethik-Kommission der Medizinischen Fakultät der Universität Wien und des Allgemeinen Krnkenhauses der Stadt Wien AKH	Wien	Austria	Univ. Prof. Dr. E Singer
Comité consultative pour la protection des personnes dans la recherché biomédicale Bordeaux B	Bordeaux	France	Prof. MC Saux
Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig	Leipzig	Germany	Prof. Dr. med. R Preiß
Ethikkommission, Campus Charité Mitte	Berlin	Germany	Prof. Dr. med. R Uebelhack
Ethik-Kommission der Ruhr- Universität Bochum, Medizinischen Fakultät	Bochum	Germany	Prof. Dr. Zenz
Ethik-Kommission der Georg-August-Ruhr-Universität Göttingen	Göttingen	Germany	Prof. Dr. med. E Rüther
Ethik-Kommission der Ärztekammer Hamburg	Hamburg	Germany	Prof. Dr. med. Th. Weber
Medizinischen Hochschule Hannover, Ethikkommission	Hannover	Germany	Prof. Dr. HD Tröger
Landesärztekammer Rheinland-Pfalz, Ethikkommission	Mainz	Germany	Prof. Dr. Rittner

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Committee Name	City	Country	Chairman
Kommission für Ethik in der ärztlichen Forschung. Bereich Humanmedizin, Klinikum der Philipps- Universität Marburg	Marburg	Germany	Prof. Dr. Med. G Richter
Regione Veneto, Aziendo Ospedaliera di Padova, Comitato Etico per la Sperimentazione	Padova	Italy	Dr. R Pegoraro
Azienda Ospedaliera Pisana, Comitato etico per la studio del farmaco sull' uomo	Pisa	Italy	Prof. R Barsotti
Regional komité for medisinsk forskninsetikk, Vest-Norge (REK Vest), Universitetet i Bergen, det medisinske fakultet	Bergen	Norway	A Berstad
Comité Ético de Investigaçáo Clinica	Porto	Portugal	
Karolinska Institutet, Forskningsettikkommitté Syd	Stockholm	Sweden	Prof. H Glaumann
Regionala etikprövningsnämnden i Stockholm	Stockholm	Sweden	Prof. LE Rutquist
Clinic Barcelona, Hospital Universitari, Comitè ètic investigaciò clinica	Barcelona	Spain	
Comité Etico de Investigación Clinica, Hospital Universitario de Getafe	Madrid	Spain	
Comité etico de investigación clinica Hospital "La Fe" Valencia	Valencia	Spain	
Northern and Yorkshire Multi-Centre Ethics Committee, Durham University	Durham	UK	J Kelly/S Brunton-Shiels
Gateshead Local research Ethics Committee	Sunderland	UK	Dr. DG Raw
Northumberland, Tyne and Wear NHS Strategic Health Authority Local Research Ethics Committees, Newcastle General Hospital	Newcastle upon Tyne	UK	Dr. J Lothian, PD Carr
Southampton & South West Hampshire Local Research Ethics Committee	Southampton	UK	C Wright
Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilans-Universität, LMU, Klinikum Großhadern	München	Germany	Prof. Dr. G Paumgartner
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig
Aligemeines öffentliches Krankenhaus der Stadt Linz, Kommission zur Beurteilung klinischer Prüfungen von Arzneimitteln, Ethikkommission	Linz	Austria	Primar Dr. H Stekel
Ospedali Civili Brescia, Aziendo Ospedaliera, Comitato Etico	Brescia	Italy	Prof. F De Ferrari

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Committee Name	City	Country	Chairman
Fakultní nemocnice v Motole, Etickákomise	Prague	Czech Republic	MUDr. V Šmelhaus
Brighton and Sussex Local Research Ethics Committee	Brighton	UK	Dr. P Seddon
East Sussex Local Research Ethics Committee	Brighton	UK	Dr. J Rademaker
South Manchester Local Research Ethics Committee	Manchester	UK	Dr. W Pettit
Central Manchester Research Ethics Committee	Manchester	UK	Dr. D Mandal
NHS Tayside Board, Tayside Committee on Medical Research Ethics, Ninewells Hospital & Medical School	Dundee	UK	NF Brown
Fazio-Fondazione San Raffaele Del Monte Tabor Milano, Comitato Etico Dell'istituto Nazionale Neurologico Besta di Milano	Milano	Italy	Prof. E Müller
IRCCS – Fondazione San Raffaele Del Monte Tabor di Milano	Milano	Italy	Prof. G Zoppei
Comité ético de investigación clínica, Servicio Andaluz de Salud, Consejería de Salud, Hospitales Universitarios Virgen de Rocío de Sevilla	Sevilla	Spain	
Ethikkommission der stadt Wien	Wien	Austria	Dr. H Serban
North Sheffield Local Research Ethics Committee, Northern General Hospital	Sheffield	UK	Dr. G PM Clark
Glasgow West Local Research Ethics Committee	Glasgow	UK	Dr. J Hunter
NHS Greater Glasgow Primary Care Division Local Research Ethics Committee, Gartnavel Royal Hospital	Glasgow	UK	Dr. P Fleming
Frenchay Research Ethics Committee, North Bristol NHS Trust Headquarters	Bristol	UK	Drs. Kendall and M Shere
Ärztekammer Berlin, Ethik-Kommission	Berlin	Germany	C Biondo
Ethikkommission des Landes Bremen, Institut für Klinische Pharmaakologie, Klinikum Bremen-Mitte	Bremen	Germany	Dr. K Boomgaarden-Brandes
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig

PDT304

Committee Name	City	Country	Chairman
Ethics Committee of the Southern General Hospital NHS Trust, Glasgow	Glasgow	UK	Rev. D Keddie

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Committee Name	City	Country	Chairman
Kommission für Ethik in der Ärztlichen Forschung, Klinikum der Philipps-Universität Marburg	Marburg	Germany	Prof. Dr. med. G Richter
New Cross Hospital Local Research Ethics Committee	Wolverhampton	UK	D S Little
Southampton and South West Hampshire Joint Local	Southampton	UK	Dr. A Kermode
Joint Ethics Committee Newcastle and North Tyneside Health Authority	Newcastle	UK	Prof. PA Heasman
Comite Etico de Investigacion Clinica Hospital Clinic I Provincial	Barcelona	Spain	Prof. J Rodes
Comite Etico de Investigacion Clinica del Hospital de la Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrenca
Comité d' éthique hospitalier, Cliniques Universitaires de Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Hospitais da Universidade de Coimbra	Coimbra	Portugal	Dr. JA Branquinho de Carvalho
Ethikkommission der Medizinischen Faultät der Universität Innsbruck	Innsbruck	Austria	Univ. Prof. Dr. P Lukas

PDT408

Committee Name	City	Country	Chairman
Hospital Ethical Committee, University Hospital UCL Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Commission for Ethics, AZ St.-Jan AV	Brugge	Belgium	Dr. J Van Droogenbroeck
Comite Consultatif de Protection des Personnes Dans La Recherche Biomedicale de Lille, Hôpital Huriez	Lille	France	Prof. PY Hatron
Ethik-Kommission der Ärztekammer Hamburg Kōrperschaft des ōffentlichen Rechts	Hamburg	Germany	Prof. Dr. Med. K Held
Ethikkomission des Klinikums der Universität Regensberg	Regensberg	Germany	Prof. Dr. R Andreesen
Vorsitzenden der Ethikkommission Bei der Ärztekammer des Saarlandes	Saarbrücken	Germany	Dr. S Ertz
Spett. Le Comitato Etico	Milano	Italy	Prof. A Randazzo
Comitato Etico Per La Sperimentazione Clinica Del Farmaci	Firenze	Italy	Prof. L Zilletti

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Committee Name	City	Country	Chairman
Ministério Da Saúde Hospitais Da Universidade De Coimbra	Coimbra	Portugal	Prof. Dr. JM Pedroso Lima
Comité Ético De Investigación Clínica Hospital Clínic I Provincial	Barcelona	Spain	Prof. MA Asenjo Sebastián
Comité Ético De Investigación Clínica Del Hospital De La Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrencá
King's College Hospital	London	UK	Prof. ER Howard
Southampton and South West Hampshire Local Research Ethics Committees	Southampton	UK	Dr. A Kermode
Etik-Kommission Der Medizinischen Faultät der Universität Wien	Wien	Austria	Univ. Prof. Dr. E Singer

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Table S3. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – PP population (N = 622)

		Study				
		DP008-003 (N = 157)	**PDT304 (N = 100)**	**PDT301 (N = 288)**	**PDT408 (N=77)**	**Total (N = 622)**
Age (yr)	Mean (SD)	63.1 (8.51)	60.5 (10.97)	74.2 (7.02)	64.1 (12.05)	67.9 (10.61)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	64.0	61.5	75.0	67.0	69.0
Gender	Male	99 (63%)	57 (57%)	160 (56%)	40 (52%)	356 (57%)
	Female	58 (37%)	43 (43%)	128 (44%)	37 (48%)	266 (43%)
Race	Caucasian	153 (97%)	100 (100%)	288 (100%)	76 (99%)	617 (99%)
	Black	3 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		115 (73%)	69 (69%)	0 (0%)	47 (61%)	231 (37%)
Possible PS		115 (73%)	5 (5%)	0 (0%)	47 (61%)	167 (27%)
Probable PS		0 (0%)	64 (64%)	0 (0%)	0 (0%)	64 (10%)
DLB (SDDD)		0 (0%)	0 (0%)	110 (38%)	0 (0%)	110 (18%)
Possible DLB		0 (0%)	0 (0%)	25 (9%)	0 (0%)	25 (4%)
Probable DLB		0 (0%)	0 (0%)	85 (30%)	0 (0%)	85 (14%)
Non-PS/Non-DLB (no SDDD)		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)
ET		16 (10%)	14 (14%)	0 (0%)	23 (30%)	53 (9%)
AD		0 (0%)	0 (0%)	122 (42%)	0 (0%)	122 (20%)
Other		26 (17%)	17 (17%)	1 (<1%)	7 (9%)	51 (8%)
SDDD Present[a]		115 (73%)	69 (69%)	110 (38%)	47 (61%)	341 (55%)
SDDD Absent		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; ET = Essential tremor; N = number of subjects in the study; PP = Per protocol; PS = Parkinsonian syndrome; SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Table S4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[a] – Baseline	91.1% (89.2 to 92.8)	92.3% (89.3 to 94.7)	78.5% (72.7 to 83.5)	90.1% (86.8 to 92.8)	88.7% (86.8 to 90.4)	91.2% (89.0 to 93.0)
Mean Results Across all Readers[b] – Month 12			78.5% (72.7 to 83.5)	92.8% (89.6 to 95.2)		
Mean Results Across all Readers[c] – Month 18	78.9% (72.8 to 84.2)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	76.6% (70.1 to 82.3)	96.7% (90.6 to 99.3)				

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Summary results calculated across all studies and readers at baseline.

[b] Summary results calculated across all readers for study PDT301.

[c] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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Table S5. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[a] – Baseline	90.0% (87.6 to 92.0)	93.7% (90.4 to 96.2)	78.5% (72.7 to 83.5)	90.3% (87.0 to 93.0)	87.3% (85.1 to 89.3)	91.7% (89.5 to 93.7)
Mean Results Across all Readers[b] – Month 12			78.3% (72.5 to 83.4)	93.0% (89.8 to 95.4)		
Mean Results Across all Readers[c] – Month 18	78.3% (72.0 to 83.7)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	75.9% (69.3 to 81.7)	96.7% (90.6 to 99.3)				

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Summary results calculated across all studies and readers at baseline.

[b] Summary results calculated across all readers for study PDT301.

[c] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-4
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	7
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	8-12, Table 1[a]
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	8-12[a]
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	8-13[a]
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	8-13[a]
Test methods	7	The reference standard and its rationale.	12-13, 24-25
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	12-13
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	12-13
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	8-13[a]
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	12-13
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	13-14
	13	Methods for calculating test reproducibility, if done.	14
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	7[a]
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Tables 1, 2, & S3
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	Figure 1
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	13
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Figure 2
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A[a]
	20	Any adverse events from performing the index tests or the reference standard.	N/A[b]
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Figs 3 & 4, Tables 3, 4, S4, & S5
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A[a]
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	23, Tables 3, 4, S4, & S5

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	24	Estimates of test reproducibility, if done.	23
DISCUSSION	25	Discuss the clinical applicability of the study findings.	24-27

[a] Since this was a pooled analysis of 4 clinical trials and each of these individual studies have been previously published, some of these details are not included in this paper with the references provided. The individual primary publications of the 4 studies were referred to to obtain these details.
[b] Safety data were not a focus of the current report and will be published in a separate report.

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD. Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

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Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging indeed has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.
    - Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

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Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis, particularly at follow-up after 12 months or later, is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. Numerous clinical trials have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[3, 13-18] However, each trial had limited numbers of subjects for whom results were available, ranging from 20 to 326.[3, 16] To better estimate the diagnostic performance of ioflupane (^{123}I), we conducted a pooled analysis of four clinical studies. These studies were selected as they are the large, pivotal, multi-site efficacy trials included in the DaTscan clinical development program. They were conducted to GCP standards in pre-defined populations, and were the ones submitted to support the NDA filing in the USA (3 of them for EU) for licensing. We did not include single site studies, small early development trials, or clinical utility studies in uncertain populations, because many of these had not evaluated DaTscan efficacy performance. Our intent was to use the original database from the NDA submission for the pooled analysis, and not to perform a meta-analysis of the published literature, because this has been done.[19, 20].

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METHODS

Participants

Four clinical trials were used for this pooled analysis, based on their similar designs and objectives; we used source data from studies performed in support of the ioflupane (^{123}I) US NDA.[3, 13-15, 17] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN™ or DaTscan™ , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[21] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304 [also elsewhere sometimes known as PDT03004]). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Dates study was conducted	• Aug 1997 to Feb 1998	• Jan 1999 to Jun 2005	• Dec 2003 to Jun 2006	• Nov 2000 to Nov 2003

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[3, 13-15, 17] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection.

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Ioflupane (^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images.

Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all

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dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

This pooled analysis of four clinical trials provides the largest set of clinical evidence to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, ioflupane (^{123}I) SPECT image evaluation demonstrated a sensitivity (ability to detect an SDDD when it is present) ranging from 75.0% to 96.5%, and a specificity (ability to exclude an SDDD when it is absent) ranging from 83.0% to 100.0%. Inter-reader agreement was high, indicating that diagnostic accuracy is not dependent upon individual expert performance.

When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 15, 22] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies (PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003,

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enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[16, 21] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[16] Therefore, the use of clinical diagnosis as the non-perfect reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy,

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with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[23] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[24] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[24] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[25] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I) imaging results became available.[6, 26] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[27, 28] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[27] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

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Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[29] The Society of Nuclear Medicine,[30] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[31] the Scottish Intercollegiate Guidelines Network (SIGN),[32] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[33] Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[18, 34, 35] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[34] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA, DLB) and tauopathies (PSP, corticobasal degeneration).[37,38]

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Literature Review and Interpretation

We searched PubMed on October 4, 2013 using the terms (*FP-CIT or *Ioflupane[Title]) AND (Lewy or dementia or parkinson* or essential tremor[Title]) AND (diagnos* or accura*[Title]) and applied the filter "Human." The search retrieved 181 articles. After reviews, case reports, and commentaries were removed, 138 remained. Of these, 28 were clinical studies that evaluated the diagnostic accuracy of ioflupane (^{123}I),[3, 13-17, 39-61] with the number of subjects ranging from 16[55] to 326.[14] We selected four of these, which were the studies that supported the US NDA. We also found in our search two meta-analyses[19, 20] of the diagnostic accuracy of ioflupane (^{123}I) in DLB and parkinsonian syndromes. The first was performed in 2012 and summarized four studies with a total of 419 subjects. One of the studies included in this meta-analysis is the PDT301 study (with the baseline clinical evaluation)[3] included in our pooled analysis. The second was performed in 2007 and summarized 32 studies, one of which was DP008-003.[13]

This pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date of the diagnostic accuracy of ioflupane (^{123}I) SPECT imaging. The analysis includes patients with dementia and/or movement disorders. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75·0% to 96·5%, and specificity ranged from 83·0% to 100·0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0·81 to 1·00. Adoption and utilization of this new technology is expanding, reinforcing the usefulness of ioflupane (^{123}I) imaging as a validated diagnostic tool.

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GE Healthcare provided funding and administrative support for this pooled analysis; managed statistical analysis, medical writing, and interpretation of the data; drafted sections of the manuscript; and reviewed, edited, and approved the manuscript.

Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies).

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

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JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

Dr. O'Brien reports grants and other from GE Healthcare, grants and other from Lilly, other from Bayer Healthcare, other from TauRx, other from Cytox, outside the submitted work.

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Dr. Grachev reports employment from GE Healthcare, during the conduct of the study.

Data sharing statement

No additional data are available.

Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

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4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD. Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

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Keywords: Parkinson's disease, Movement disorders, Dementia, SPECT, Neuroradiology

Primary Subject Heading: Neurology

Secondary Subject Heading: Radiology and imaging

Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging indeed has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.

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- Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis, particularly at follow-up after 12 months or later, ~~though the standard of expert clinical diagnosis used~~ is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. Numerous clinical trials have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[3, 13-18] However, each trial had limited numbers of subjects for whom results were available, ranging from 20 to 326.[3, 16] To better estimate the diagnostic performance of ioflupane (^{123}I), we conducted a pooled analysis of four clinical studies. These studies were selected as they are the large, pivotal, multi-site efficacy trials included in the DaTscan clinical development program. They were conducted to GCP standards in pre-defined populations, and were the ones submitted to support the NDA filing in the USA (3 of them for EU) for licensing. We did not include single site studies, small early development trials, or clinical utility studies in uncertain populations, because many of these had not evaluated DaTscan efficacy performance. Our intent was to use the original database from the NDA submission for the pooled analysis, and not to perform a meta-analysis of the published literature, because this has been done.[19, 20].

~~Four clinical trials (three Phase 3 and one Phase 4) performed to support the US New Drug Application (NDA) were chosen for this pooled analysis because of their similar designs,~~

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~~methodologies, endpoints, and patient populations. It should be noted that this is a pooled analysis, and is not a meta-analysis of peer-reviewed publications.~~

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METHODS

Participants

Four clinical trials were used for this pooled analysis, based on their similar designs and objectives; we used source data from studies performed in support of the ioflupane (^{123}I) US NDA.[3, 13-15, 17] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[~~19~~21] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304 [also elsewhere sometimes known as PDT03004]). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. ~~PDT03004 is also known as PDT304, and will be referred to as PDT304 throughout this paper.~~ Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Dates study was conducted	• Aug 1997 to Feb 1998	• Jan 1999 to Jun 2005	• Dec 2003 to Jun 2006	• Nov 2000 to Nov 2003

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[3, 13-15, 17] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection.

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Ioflupane (^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images.

Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all

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dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

This pooled analysis of four clinical trials provides the largest set of clinical evidence to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, ioflupane (^{123}I) SPECT image evaluation demonstrated a sensitivity (ability to detect an SDDD when it is present) ranging from 75.0% to 96.5%, and a specificity (ability to exclude an SDDD when it is absent) ranging from 83.0% to 100.0%. Inter-reader agreement was high, indicating that diagnostic accuracy is not dependent upon individual expert performance.

When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 15, 2220] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies (PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003,

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enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[16, ~~19~~21] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[16] Therefore, the use of clinical diagnosis as the non-perfect reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy,

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with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[~~21~~23] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[~~22~~24] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[~~22~~24] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[~~23~~25] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I) imaging results became available.[6, ~~24~~26] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[~~25~~27, ~~26~~28] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[~~25~~27] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

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Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[~~27~~29] The Society of Nuclear Medicine,[~~28~~30] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[~~29~~31] the Scottish Intercollegiate Guidelines Network (SIGN),[~~30~~32] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[~~31~~33]

Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[18, ~~32~~34, ~~33~~35] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[34] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA,

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DLB) and tauopathies (PSP, corticobasal degeneration).[~~35~~37,~~36~~38]

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Literature Review and Interpretation

We searched PubMed on October 4, 2013 using the terms (*FP-CIT or *Ioflupane[Title]) AND (Lewy or dementia or parkinson* or essential tremor[Title]) AND (diagnos* or accura*[Title]) and applied the filter "Human." The search retrieved 181 articles. After reviews, case reports, and commentaries were removed, 138 remained. Of these, 28 were clinical studies that evaluated the diagnostic accuracy of ioflupane (^{123}I),[3, 13-17, ~~37~~39-~~59~~61] with the number of subjects ranging from 16[~~53~~55] to 326.[14] We selected four of these, which were the studies that supported the US NDA. We also found in our search ~~a~~two meta-analys~~i~~es[~~60~~19, 20] of the diagnostic accuracy of ioflupane (^{123}I) in DLB and parkinsonian syndromes. The first was performed in 2012 and summarized four studies with a total of 419 subjects. One of the studies included in this meta-analysis is the PDT301 study (with the baseline clinical evaluation)[3] included in our pooled analysis. The second was performed in 2007 and summarized 32 studies, one of which was DP008-003.[13]

This pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date of the diagnostic accuracy of ioflupane (^{123}I) SPECT imaging. The analysis includes patients with dementia and/or movement disorders. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75·0% to 96·5%, and specificity ranged from 83·0% to 100·0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0·81 to 1·00. Adoption and utilization of this new technology is expanding, reinforcing the usefulness of ioflupane (^{123}I) imaging as a validated diagnostic tool.

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Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies).

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

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WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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GE Healthcare provided funding and administrative support for this pooled analysis; managed statistical analysis, medical writing, and interpretation of the data; drafted sections of the manuscript; and reviewed, edited, and approved the manuscript.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

Dr. O'Brien reports grants and other from GE Healthcare, grants and other from Lilly, other from Bayer Healthcare, other from TauRx, other from Cytox, outside the submitted work.

Dr. Oertel reports grants and personal fees from GE Healthcare, personal fees from Amersham.Buchler, outside the submitted work.

Dr. McKeith reports grants and personal fees from GE Healthcare, outside the submitted work.

Dr. Grosset reports grants and personal fees from GE Healthcare, during the conduct of the study.

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Dr. Walker reports personal fees from GE Healthcare, personal fees from Bayer Healthcare, grants from GE Healthcare, grants from Lundbeck, other from GE Healthcare, and personal fees from Novartis, outside the submitted work.

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Dr. Sherwin reports other (salary) from GE Healthcare, during the conduct of the study; other (salary) from GE Healthcare, outside the submitted work.

Dr. Grachev reports employment from GE Healthcare, during the conduct of the study.

Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

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Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

Data sharing statement

Informed consent was not obtained from study participants for data sharing, but the presented data are anonymized and risk of identification is low. No additional data are available.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

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4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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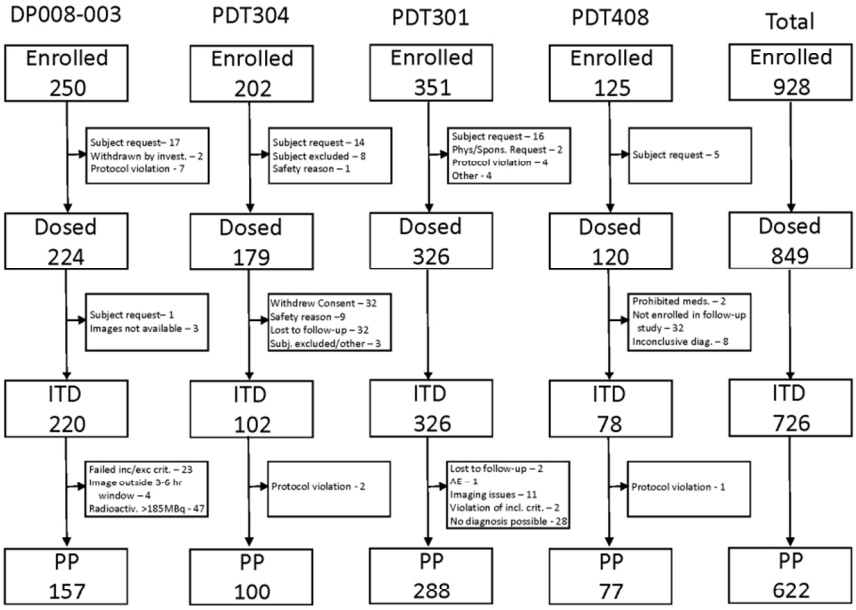

Note: Subjects may have more than one reason for discontinuing.

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Fig. 2a

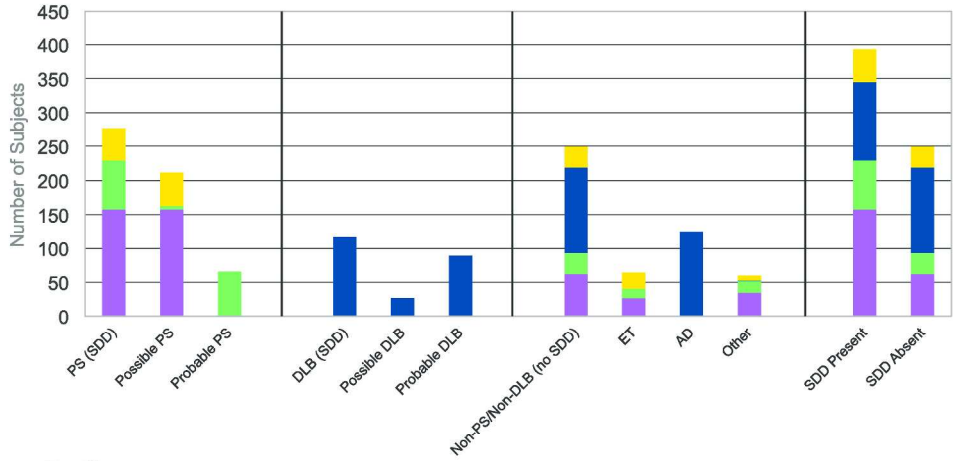
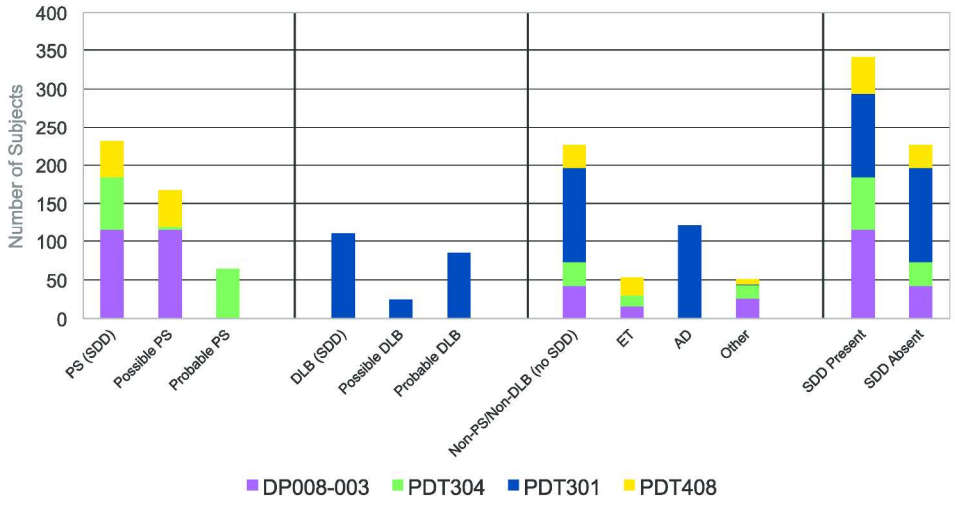


Fig. 2b



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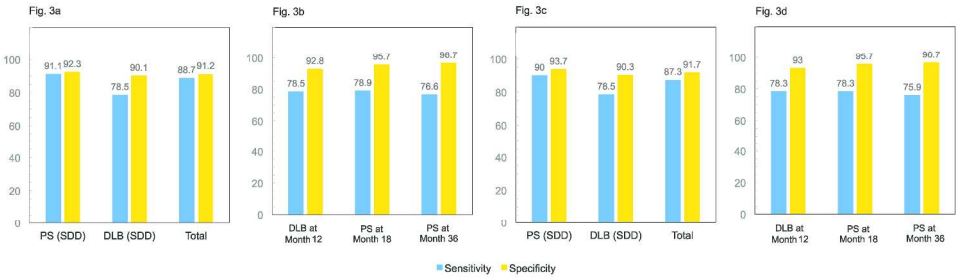

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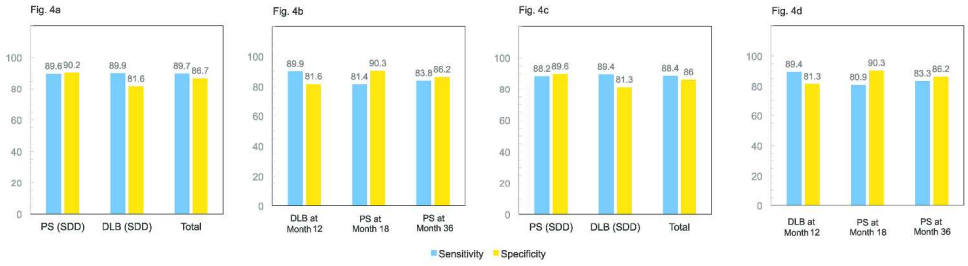

479x130mm (300 x 300 DPI)

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Table S1. Investigators who participated in the four clinical trials in this pooled analysis.

DP008-003	
Prof. EA van Royen, MD, PhD	AMC: University of Amsterdam Medical Centre (Academisch Medisch Centrum), Director of Department of Nuclear Medicine
Prof. Dr. WH Oertel	Chairman and Professor of Neurology, Department of Neurology, Klinikum, Philipps-University, Marburg, Germany
Prof. Dr. K Joseph	[Klinisch orientierte Tätigkeit auf dem Gesamtgebeit der Nuklearmedizin: 192 wissenschaftliche Veröffentlichungen]
Prof. Dr. K Tatsch	Department of Nuclear Medicine, Klinikum Grosshadern, University of Munich, Marchioninistr. 15, 81377, Munich, Germany
Dr. J Schwarz	Neurologische Klinik, Universität Ulm, 89081 Ulm
Dr. T Schwarzmüller, Dr. R Linke	University of Munich, Department of Nuclear Medicine, Klinikum Grosshadern, Marchioninistr. 15, 81377 Munich, Germany
Dr. A Storch	University of Ulm, Department of Neurology, Oberer Eselsberg 45, 89081 ULM, Germany
Dr. V Ries	Tätigkeit als Arzt im Praktikum an der Neurologischen Universitätklinik Ulm
Ms. A Gerstner	Tätigkeit als studentische Hilfskraft auf der internistisch/neurologischen Intensivstation des St. Josef-Hospitals Bochum
Ms. S Rura	Erstellung einer Doktorarbeit in der Arbeitsgruppe von Prof. Dr. W Oertel mit der Thematik Neuroprotektion im Parkinson-Tiermodell, Marburg
Dr. H Höffken (MD)	Abteilung fur Klinische Nuklearmedizin, Zentrum Radiologie des Klinkums der Phippsuniversität Marburg, Baldingerstraβe, 35033 Marburg
Dr. O Pogarell	Department of Neurology, University of Marburg, Rudolf-Biltmann-Str. 8, D-35033 Marburg, Germany
Dr. H Fritsch	Strahlenschutzbeauftragter der Abteilung für Klinische Nuklearmedizin, Steinweg 7, 35096 Weimar/Lahn
Dr. D Grosset (BSc, MD, FRCP)	Consultant Neurologist, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Govan Road, Glasgow, G51 4TF
Dr. J Patterson (BSc, PhD, MIPEM)	Principal Physicist, Department of Clinical Physics, Institute of Neurological Sciences, Southern General Hospital NHS Trust, Glasgow, G51 4TF and Honorary Research Assistant, University of Glasgow, Glasgow G12 8QQ Scotland
Dr. H Ben Amer (M.B B.ch, MRCP (UK)	
T Murphy RGN	Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, 1345 Govan Road, Glasgow, GF1 4TF
Dr. JD Speelman	
Dr. MWIM Horstink (MD, PhD)	University of Nijmegen
Dr. J Booij	AMC, the Netherlands
Dr. J Versijpt	Hoekskensstraat 130, 9080 Lochristie (getting PhD w/ Dr. Dierckx)
Dr. A Van den Eeckhaut	Essestraat 83, 9340 Lede (w/ Dr. Dierckx)
Dr. AJ Lees (MB BS, MRCP [UK], MD, FRCP)	Consultant Neurologist to the National Hospital for Neurology and Neurosurgery and University College London Hospitals….

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Dr. DC Costa (MD, MSc, PhD, FRCR Dr. M Doder Dr. H Sips	Institute of Nuclear Medicine, University College London Medical School, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK
Prof. R Dierckx	Division of Nuclear Medicine, University Hospital Gent, De Pintelaan 185, B-9000 Gent, Belgium
Dr. D Decoo	UZ Gent, Dienst Neurologie, De Pintelaan 185, 9000-GENT
Dr. C Van Der Linden	Department of Neurology, University Hospital Gent, Gent, Belgium
Dr. Rhiannon Rowsell, Dr. R Robison, Mrs. B McDougall, Mrs. V Thody	Nycomed Amersham plc, White Lion Road, Little Chalfont, Buckinghamshire, HP7 9NA, UK
Dr. T Frear	Frear and Associates, 77 Benetfeld Road, Foxley Fields, Binfield, Berkshire, RG42 4EW, UK
Mrs. M Cobb	Nycomed Imaging, Clinical Research Associate, Nycomed Amersham plc, White Lion Road, Little Chalfont, Buckinghamshire, HP7 9NA, UK
Mrs. R Sakowski	General Manager/Clinical Trials Manager, Chiltern International GmbH, Ober-Eschbacher Straβe 91, 61352 Bgd Homburg v.d.H. Germany
Dr. C Deubelbeiss (PhD)	Clinical Research Associate, Chiltern International GmbH, Berner Str. 49, D-60437 Frankfurt, Germany
Dr. M Titulaer, Dr. M Al (MSc x 2, PhD)	Farma Research BV, Nijmegen (CRO), the Netherlands
HJW Adrianus (PhD?)	Als arts-assistant neurologie Radboudziekenhuis te Nijmegen
Svetislav Gacinovic (MsC, MD)	Institute of Nuclear Medicine, University College London Medical School, Mortimer Street, London, W1A 8AA, UK
PDT301	
Kendle GmbH & Co. GMI KG	Georg-Brauchle-Ring 6, 81929 München, Germany
Pharm-Olam International (UK) Ltd	The Brackens, London Road, Ascot, Berkshire, RG42 7UT, UK
Pharm-Olam International (UK) Ltd,	Jihovychodni VII, No. 11/928, 141 00 Prague 4, Zabehlice, Czech Republic
Phidea S.p.A.	Via C. Colombo 1, 20094 Corsico, Italy
Prof. Dr. Franz Aichner	OÖ Landesnervenklinik, Neurologische Abteilung, Wagner-Jauregg-Weg 15, 4020 Linz, Austria
Prof. Dr. Susanne Asenbaum	Universitätshospital Wien, Abteilung Neurologie, Währinger Gürtel 18-20a, 1090 Wien, Austria
Prof. Dr. Jean M. Orgogozo	Université Bordeaux, Hôpital Pellegrin, Place Amélie Raba Léon, 33076 Bordeaux, France
Prof. Dr. Florence Pasquier	Hôpital Roger Salengro, Rue Prof Emile Laine, 59000 Lille, France

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Prof. Dr. Johannes Schwarz	Klinik und Poliklinik für Neurologie, Universitätsklinikum Leipzig, Liebigstr. 22a, 04103 Leipzig, Germany
Dr. Guy Arnold, PD Dr., Eike Spruth, PD Dr.	Humbold-Universität Berlin, Medizinische Fakultät Charité Mitte, Abteilung Neurologie, Schumannstr. 21, 10117 Berlin, Germany
Dr. Prof. Thomas Müller	St. Josef-Hospital, Ruhr-Universität Bochum, Gudrunstr. 56, 44791 Bochum, Germany
Dr. Inga Zerr	Georg-August Universität Göttingen, Abteilung Neurologie, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Prof. Dr. Cornelius Weiller, Prof. Dr. Achim Liepert	Universitätsklinikum Eppendorf, Klinik und Poliklinik für Neurologie, Martinistr. 52 / N24, 20246 Hamburg, Germany
Prof. Dr. Reinhard Dengler	Neurologische Klinik mit klinischer Neurophysiologie, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
PD Dr. Peter Urban, Dr. Andreas Fellgiebel	Johannes-Gutenberg Universität Mainz, Klinik und Poliklinik für Neurologie, Langenbeckstr. 1, 55101 Mainz, Germany
Prof. Dr. Wolfgang Oertel	Klinikum der Phillips-Universität Marburg, Abteilung Neurologie, Rudolf-Bultmann-Str. 8, 35039 Marburg, Germany
Prof. Dr. Gilberto Pizzolato, Dr Gianluigi Ricchierieri	Clinica Neurologica 1 – Departimento di Neuroscienze, Universitá di Padova, Via Giustiniani 5, 35128 Padova, Italy
Prof. Dr. Ubaldo Bonucelli	U.O. di Neurologia – Departimento di Neurologia, Universitá di Pisa, P.O. Santa Chiara – A.O. Pisana, Via Bonanno 54, 56126 Pisa, Italy
Prof. Dr. Dag Aarsland	Stavanger Universitetssjukehus, Dept: Psykiatrisk Klinikk, Alderspsykiatrisk Poliklinikk, PO Box 1163 Hillevåg, 4095 Stavanger, Norway
Dr. Maria M Pareira Costa	HPP Medicina Molecular, SA, Avenida da Boavista, 119, 4050-115 Porto, Portugal
Prof. Dr. Lars-Olof Wahlund	Karolinska Universitetssjukhuset, Huddinge, Hälsovägen, Flemingsberg, 14186 Stockholm, Sweden
Dr. Eduardo Tolosa Sarro	Hospital Clinic i Provincial, Unidad Memoria-Alzheimer, c/Villaroel, 170, 08036 Barcelona, Spain
Dr. Lorenzo Morlán Gracía	Hospital Universitario de Getafe, Servicio de Neurologia, Ctra. De Toledo km 12,5, 28950 Getafe, Madrid, Spain
Dr. J Andrés Burguera	Hospital Universitarion La Fe, Consultas de Neurologia. Planta Baja, Avda Campanar, 21, 46009 Valencia, Spain
Dr. Thomas Alan	Old Age Psychiatry Offices, Bensham General Hospital, Saltwell Road, Gateshead, NE8 4Yl, UK
Dr. Clive Holmes	Memory Study and Research Centre, Moorgreen Hospital, Botley, West End, Southampton, Hampshire, SO30 3JB, UK
Prof. Dr. Adrian Danek	Klinikum Großhadern der Ludwig-Maximilians-Universität, Klinik und Poliklinik für Neurologie, Marchioninistr. 15, 81377 München, Germany
Prof. Dr. Gerhard Ransmayr	Allgemeines Krankenhaus Linz, Abteilung Neurologie und Psychiatrie, Krankenhausstr. 9, 4021 Linz, Austria
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Prof. Dr. Alberto Albanese	Istituto Nazionale Neurologico “Besta”, Università Cattolica del Sacro Cuore, Via Caloria 11, 20133 Milano, Italy
Dr. Eulegio Gil Neciga	Hospital Virgen del Rocio, Neurologie, Avd de Manuel Siurot s/n, 41013 Sevilla, Spain
Ordination Dr. Michael Rainer	Lainzerstr. 20, 1130 Wien, Austria
Dr. Peter Bowie	Longley Centre, Norwood Grange Drive, Sheffield, S5 7JT, UK
Prof. Dr. Gordon Wilcock	BRACE Centre, Blackberry Hill Hospital, Fishponds, Bristol, BS16 2EW, UK
Dr. Rainhard Ehret	Schloßstr. 29, 12163 Berlin, Germany
Prof. Dr. Alexander Kurz	Psychiatrische Klinik der TU München, Moehlstr. 26, 81675 München, Germany
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Prof. Dr. Jacques Darcourt	Laboratoire de Biophysique et Traitement de l’Image, Faculte de Medicine, Universitede Nice Sophia-Antipolis, 28 Avenue de Valombrose, 06107 Nice, Cedex 2, France
Prof. Dr. Klaus Tatsch	Ludwig-Maximilians Universität, Klinikum Großhadern, Abteilung für Nuklearmedizin, Marchioninistrasse 15, D-81377 München
Dr. Frode Willoch	Aker sykehus, Radiologisk avdeling, Trondheimsveien 235, 0514 Oslo, Norway
Dr. Zuzana Walker	University College London, Department of Mental Health Sciences, 48 Riding House Street, London, Win8AA, UK
Prof. Dr. Ian McKeith, Prof. Dr. John O'Brien	Newcastle General Hospital, Institute for Health and Aging, Newcastle uponTyne, NE4, 6BE, UK
CRL.Medinet (Europe)	Bergschot 71, P.O. Box 5510, 4801 DM Breda, The Netherlands
PDT304	
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Angela O'Donnell, Mary Theresa Hansen, Bianca Holmes, David Brown, Tracey Jones, Katherine Grosset, Marlene Smeaton, Donald Hadley, Kate MacFarlane Bryce, Elaine Tyrell	
Prof. W Oertel, Anja Gerstner, Helmut Höffken, Prof. Joseph, Meike L Schipper, Doris Lang Pfeiffer, Aline Metz, Andreas Fischer, Martin Gotthardt, Sylvia Rura, Halina Pollum, Thomas Behr	Klinikum der Phillips - Universität Marburg, Med Zentrum for Nervenheilkunde, Klinik für Neurologie, Rudolf-Bultmann - Strasse 8, D 35039 Marburg, Germany
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Dr. Paul Kemp, Lucy Bolton, Helen Roberts, James Thom, Ian Gove, Livia Bolt, John S. Fleming, Sandra Johns, Maureen Zivanovic, Syed Zaman	Dept Nuclear Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
Dr. David Burn, John Fenwick, Andrea Stutt, Una Brechany, Susan Faulkner, Sophie Molloy,	Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK

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Prof W Poewe, Prof Roy Moncayo, Georg Riccabona, Eveline M Donnemiller, Klaus Seppi, Boris Becket Aurel, Clemens Decristoforo, Michael Gabriel, Dirk Rudiger Hente	Leopold-Franzens-Universität, Innsbruck, Universitätsklinikum für Neurologie, Anichstr. 35, A-6020 Innsbruck, Austria
PDT408	
Prof. Eduardo Tolosa	Dept of Neurology, H. Clinic I Provincial, Barcelona, Spain
Dr. Ana Catafau	Dept of Nuclear Medicine, H. Sant Pau, Barcelona, Spain
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Michel Van Zandijcke, Frank De Geeter	AZ St Jan, Ruddershove 10, B-8000, BRUGGE, Belgium
Alain Destee, Marc Steinling	Hôpital Roger Salengro-CHU de Lille, Rue du 8 Mai 1945, 59037 LILLE cedex, France
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Ulrich Bogdahn, Chr. Eilles	Universität Regensburg, Klinik und Poliklinik für Neurologie im Bezirksklinikum, Universistraβe 84, D-93053 REGENSBURG, Klinikum der Universitat Regensburg, Abt. f. Nuklearmedizin, Franz-Josf-Strauβ-Allee 11, D-93053 REGENSBURG, Germany
Anton Haas, Carl-Martin Kirsch	Universitätskliniken des Saarlandes, Kirrberger Straβe, D-66421, HOMBURG/SAAR, Germany
Angelo Antonini, Riccardo Benti	Centro Parkinson, C.T.O., Az. Osp. Istituti Clinici di Perfezionamento, Via Bignami 1, I-20126 MILAN, Ospedale Maggiore di Milano, I.R.C.C.S., Padiglione Granelli, Via F. Sforza 35, I-20122 MILAN, Italy
Sandro Sorbi, Alberto Pupi	Università di Firenze, Viale Morgagni 85, I-50134 FLORENCE, Italy
Luis Cunha, João Pedroso de Lima	Hospitais da Universidade de Coimbra, Av. Bissaya Barreto, P-3000-075 COIMBRA
Eduardo Tolosa, Francisco Lomeña	Hospital Clinic i Provincial, Villarroel, 170, E-08036 BARCELONA, Spain
Jaime Kulisevsky, Ana M Catafau	Hospital de la Santa Creu i Sant Pau, Paseo San Antonio María Claret, 167, E-08025 BARCELONA, Spain
Ray Chaudhuri, Muriel Buxton-Thomas	King's College Hospital, Denmark Hill, CAMBERWELL, SE5 9RS, UK
William RG Gibb, Paul M Kemp	Southampton General Hospital, Tremona Road, SOUTHAMPTON S016 6YD, UK
Susanne Asenbaum, Robert Dudczak	Allgemeines Krankenhaus der Stadt Wien, Währingergürtel 18-20, A-1090 VIENNA, Austria

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Table S2. Ethics Committees for the Four Studies in the Pooled Analysis

Study DP008-003

Committee Name	City	Country	Chairman
Medical Research Ethics Committee, The Phillips University Clinic	Marburg	Germany	Dr. P Heubel
The Faculty of Medicine Ethics Committee, Ludwig Maximilian University of Munich	Munich	Germany	Prof. Dr. med. Dent. W Gernet
Southern General Hospital Medical Ethics Committee	Glasgow	UK	Rev. D Keddie
Medical Ethics Committee, Academic Medical Center, Amsterdam University	Amsterdam	The Netherlands	Prof. L Arisz
Joint UCL/UCLH Committees on the Ethics of Human Research	London	UK	Prof. A McLean
Ethics Review Committee, University Hospital	Ghent	Belgium	Prof. Dr. M Bogaert

PDT301

Committee Name	City	Country	Chairman
Ethikkommission des Landes Oberösterreich	Linz	Austria	Univ. Prof. Prim Dr. Fisher
Ethik-Kommission der Medizinischen Fakultät der Universität Wien und des Allgemeinen Krnkenhauses der Stadt Wien AKH	Wien	Austria	Univ. Prof. Dr. E Singer
Comité consultative pour la protection des personnes dans la recherché biomédicale Bordeaux B	Bordeaux	France	Prof. MC Saux
Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig	Leipzig	Germany	Prof. Dr. med. R Preiß
Ethikkommission, Campus Charité Mitte	Berlin	Germany	Prof. Dr. med. R Uebelhack
Ethik-Kommission der Ruhr- Universität Bochum, Medizinischen Fakultät	Bochum	Germany	Prof. Dr. Zenz
Ethik-Kommission der Georg-August-Ruhr-Universität Göttingen	Göttingen	Germany	Prof. Dr. med. E Rüther
Ethik-Kommission der Ärztekammer Hamburg	Hamburg	Germany	Prof. Dr. med. Th. Weber
Medizinischen Hochschule Hannover, Ethikkommission	Hannover	Germany	Prof. Dr. HD Tröger
Landesärztekammer Rheinland-Pfalz, Ethikkommission	Mainz	Germany	Prof. Dr. Rittner

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Committee Name	City	Country	Chairman
Kommission für Ethik in der ärztlichen Forschung. Bereich Humanmedizin, Klinikum der Philipps- Universität Marburg	Marburg	Germany	Prof. Dr. Med. G Richter
Regione Veneto, Aziendo Ospedaliera di Padova, Comitato Etico per la Sperimentazione	Padova	Italy	Dr. R Pegoraro
Azienda Ospedaliera Pisana, Comitato etico per la studio del farmaco sull' uomo	Pisa	Italy	Prof. R Barsotti
Regional komité for medisinsk forskninsetikk, Vest-Norge (REK Vest), Universitetet i Bergen, det medisinske fakultet	Bergen	Norway	A Berstad
Comité Ético de Investigação Clinica	Porto	Portugal	
Karolinska Institutet, Forskningsettikkommitté Syd	Stockholm	Sweden	Prof. H Glaumann
Regionala etikprövningsnämnden i Stockholm	Stockholm	Sweden	Prof. LE Rutquist
Clinic Barcelona, Hospital Universitari, Comitè ètic investigaciò clinica	Barcelona	Spain	
Comité Etico de Investigación Clinica, Hospital Universitario de Getafe	Madrid	Spain	
Comité etico de investigación clinica Hospital "La Fe" Valencia	Valencia	Spain	
Northern and Yorkshire Multi-Centre Ethics Committee, Durham University	Durham	UK	J Kelly/S Brunton-Shiels
Gateshead Local research Ethics Committee	Sunderland	UK	Dr. DG Raw
Northumberland, Tyne and Wear NHS Strategic Health Authority Local Research Ethics Committees, Newcastle General Hospital	Newcastle upon Tyne	UK	Dr. J Lothian, PD Carr
Southampton & South West Hampshire Local Research Ethics Committee	Southampton	UK	C Wright
Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilans-Universität, LMU, Klinikum Großhadern	München	Germany	Prof. Dr. G Paumgartner
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig
Aligemeines öffentliches Krankenhaus der Stadt Linz, Kommission zur Beurteilung klinischer Prüfungen von Arzneimitteln, Ethikkommission	Linz	Austria	Primar Dr. H Stekel
Ospedali Civili Brescia, Aziendo Ospedaliera, Comitato Etico	Brescia	Italy	Prof. F De Ferrari

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Committee Name	City	Country	Chairman
Fakultní nemocnice v Motole, Etickákomise	Prague	Czech Republic	MUDr. V Šmelhaus
Brighton and Sussex Local Research Ethics Committee	Brighton	UK	Dr. P Seddon
East Sussex Local Research Ethics Committee	Brighton	UK	Dr. J Rademaker
South Manchester Local Research Ethics Committee	Manchester	UK	Dr. W Pettit
Central Manchester Research Ethics Committee	Manchester	UK	Dr. D Mandal
NHS Tayside Board, Tayside Committee on Medical Research Ethics, Ninewells Hospital & Medical School	Dundee	UK	NF Brown
Fazio-Fondazione San Raffaele Del Monte Tabor Milano, Comitato Etico Dell'istituto Nazionale Neurologico Besta di Milano	Milano	Italy	Prof. E Müller
IRCCS – Fondazione San Raffaele Del Monte Tabor di Milano	Milano	Italy	Prof. G Zoppei
Comité ético de investigación clínica, Servicio Andaluz de Salud, Consejería de Salud, Hospitales Universitarios Virgen de Rocío de Sevilla	Sevilla	Spain	
Ethikkommission der stadt Wien	Wien	Austria	Dr. H Serban
North Sheffield Local Research Ethics Committee, Northern General Hospital	Sheffield	UK	Dr. G PM Clark
Glasgow West Local Research Ethics Committee	Glasgow	UK	Dr. J Hunter
NHS Greater Glasgow Primary Care Division Local Research Ethics Committee, Gartnavel Royal Hospital	Glasgow	UK	Dr. P Fleming
Frenchay Research Ethics Committee, North Bristol NHS Trust Headquarters	Bristol	UK	Drs. Kendall and M Shere
Ärztekammer Berlin, Ethik-Kommission	Berlin	Germany	C Biondo
Ethikkommission des Landes Bremen, Institut für Klinische Pharmaakologie, Klinikum Bremen-Mitte	Bremen	Germany	Dr. K Boomgaarden-Brandes
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig

PDT304

Committee Name	City	Country	Chairman
Ethics Committee of the Southern General Hospital NHS Trust, Glasgow	Glasgow	UK	Rev. D Keddie

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Committee Name	City	Country	Chairman
Kommission für Ethik in der Ärztlichen Forschung, Klinikum der Philipps-Universität Marburg	Marburg	Germany	Prof. Dr. med. G Richter
New Cross Hospital Local Research Ethics Committee	Wolverhampton	UK	D.S.Little
Southampton and South West Hampshire Joint Local	Southampton	UK	Dr. A Kermode
Joint Ethics Committee Newcastle and North Tyneside Health Authority	Newcastle	UK	Prof. PA Heasman
Comite Etico de Investigacion Clinica Hospital Clinic I Provincial	Barcelona	Spain	Prof. J Rodes
Comite Etico de Investigacion Clinica del Hospital de la Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrenca
Comité d' éthique hospitalier, Cliniques Universitaires de Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Hospitais da Universidade de Coimbra	Coimbra	Portugal	Dr. JA Branquinho de Carvalho
Ethikkommission der Medizinischen Faultät der Universität Innsbruck	Innsbruck	Austria	Univ. Prof. Dr. P Lukas

PDT408

Committee Name	City	Country	Chairman
Hospital Ethical Committee, University Hospital UCL Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Commission for Ethics, AZ St.-Jan AV	Brugge	Belgium	Dr. J Van Droogenbroeck
Comite Consultatif de Protection des Personnes Dans La Recherche Biomedicale de Lille, Hôpital Huriez	Lille	France	Prof. PY Hatron
Ethik-Kommission der Ärztekammer Hamburg Kōrperschaft des ōffentlichen Rechts	Hamburg	Germany	Prof. Dr. Med. K Held
Ethikkomission des Klinikums der Universität Regensberg	Regensberg	Germany	Prof. Dr. R Andreesen
Vorsitzenden der Ethikkommission Bei der Ärztekammer des Saarlandes	Saarbrücken	Germany	Dr. S Ertz
Spett. Le Comitato Etico	Milano	Italy	Prof. A Randazzo
Comitato Etico Per La Sperimentazione Clinica Del Farmaci	Firenze	Italy	Prof. L Zilletti

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Ministério Da Saúde Hospitais Da Universidade De Coimbra	Coimbra	Portugal	Prof. Dr. JM Pedroso Lima
Comité Ético De Investigación Clínica Hospital Clínic I Provincial	Barcelona	Spain	Prof. MA Asenjo Sebastián
Comité Ético De Investigación Clínica Del Hospital De La Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrencá
King's College Hospital	London	UK	Prof. ER Howard
Southampton and South West Hampshire Local Research Ethics Committees	Southampton	UK	Dr. A Kermode
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Table S3. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – PP population (N = 622)

		Study				
		DP008-003 (N = 157)	**PDT304 (N = 100)**	**PDT301 (N = 288)**	**PDT408 (N=77)**	**Total (N = 622)**
Age (yr)	Mean (SD)	63.1 (8.51)	60.5 (10.97)	74.2 (7.02)	64.1 (12.05)	67.9 (10.61)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	64.0	61.5	75.0	67.0	69.0
Gender	Male	99 (63%)	57 (57%)	160 (56%)	40 (52%)	356 (57%)
	Female	58 (37%)	43 (43%)	128 (44%)	37 (48%)	266 (43%)
Race	Caucasian	153 (97%)	100 (100%)	288 (100%)	76 (99%)	617 (99%)
	Black	3 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		115 (73%)	69 (69%)	0 (0%)	47 (61%)	231 (37%)
Possible PS		115 (73%)	5 (5%)	0 (0%)	47 (61%)	167 (27%)
Probable PS		0 (0%)	64 (64%)	0 (0%)	0 (0%)	64 (10%)
DLB (SDDD)		0 (0%)	0 (0%)	110 (38%)	0 (0%)	110 (18%)
Possible DLB		0 (0%)	0 (0%)	25 (9%)	0 (0%)	25 (4%)
Probable DLB		0 (0%)	0 (0%)	85 (30%)	0 (0%)	85 (14%)
Non-PS/Non-DLB (no SDDD)		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)
ET		16 (10%)	14 (14%)	0 (0%)	23 (30%)	53 (9%)
AD		0 (0%)	0 (0%)	122 (42%)	0 (0%)	122 (20%)
Other		26 (17%)	17 (17%)	1 (<1%)	7 (9%)	51 (8%)
SDDD Present[a]		115 (73%)	69 (69%)	110 (38%)	47 (61%)	341 (55%)
SDDD Absent		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; ET = Essential tremor; N = number of subjects in the study; PP = Per protocol; PS = Parkinsonian syndrome; SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Table S4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[a] – Baseline	91.1% (89.2 to 92.8)	92.3% (89.3 to 94.7)	78.5% (72.7 to 83.5)	90.1% (86.8 to 92.8)	88.7% (86.8 to 90.4)	91.2% (89.0 to 93.0)
Mean Results Across all Readers[b] – Month 12			78.5% (72.7 to 83.5)	92.8% (89.6 to 95.2)		
Mean Results Across all Readers[c] – Month 18	78.9% (72.8 to 84.2)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	76.6% (70.1 to 82.3)	96.7% (90.6 to 99.3)				

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Summary results calculated across all studies and readers at baseline.

[b] Summary results calculated across all readers for study PDT301.

[c] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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Table S5. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[a] – Baseline	90.0% (87.6 to 92.0)	93.7% (90.4 to 96.2)	78.5% (72.7 to 83.5)	90.3% (87.0 to 93.0)	87.3% (85.1 to 89.3)	91.7% (89.5 to 93.7)
Mean Results Across all Readers[b] – Month 12			78.3% (72.5 to 83.4)	93.0% (89.8 to 95.4)		
Mean Results Across all Readers[c] – Month 18	78.3% (72.0 to 83.7)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	75.9% (69.3 to 81.7)	96.7% (90.6 to 99.3)				

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Summary results calculated across all studies and readers at baseline.

[b] Summary results calculated across all readers for study PDT301.

[c] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-4
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	7
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	8-12, Table 1[a]
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	8-12[a]
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	8-13[a]
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	8-13[a]
Test methods	7	The reference standard and its rationale.	12-13, 24-25
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	12-13
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	12-13
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	8-13[a]
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	12-13
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	13-14
	13	Methods for calculating test reproducibility, if done.	14
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	7[a]
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Tables 1, 2, & S3
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	Figure 1
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	13
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Figure 2
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A[a]
	20	Any adverse events from performing the index tests or the reference standard.	N/A[b]
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Figs 3 & 4, Tables 3, 4, S4, & S5
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A[a]
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	23, Tables 3, 4, S4, & S5

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	24	Estimates of test reproducibility, if done.	23
DISCUSSION	25	Discuss the clinical applicability of the study findings.	24-27

[a] Since this was a pooled analysis of 4 clinical trials and each of these individual studies have been previously published, some of these details are not included in this paper with the references provided. The individual primary publications of the 4 studies were referred to to obtain these details.
[b] Safety data were not a focus of the current report and will be published in a separate report.

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BMJ Open

Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Secondary Subject Heading:	Radiology and imaging
Keywords:	Dementia < NEUROLOGY, Neuroradiology < RADIOLOGY & IMAGING, Parkinson-s disease < NEUROLOGY

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial. These four trials were selected because they were the four pivotal studies used for the US new drug application to the FDA.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD.

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Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

Abstract word count: 232

Funding: GE Healthcare (Princeton, NJ).

Keywords: Parkinson's disease, Movement disorders, Dementia, SPECT, Neuroradiology

Primary Subject Heading: Neurology

Secondary Subject Heading: Radiology and imaging

Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging indeed has high sensitivity and specificity for detecting the presence or absence of a striatal

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dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.

- Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis, particularly at follow-up after 12 months or later, is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration (FDA) approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. Numerous clinical trials have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[3, 13-18] However, each trial had limited numbers of subjects for whom results were available, ranging from 20 to 326.[3, 16] To better estimate the diagnostic performance of ioflupane (^{123}I), we conducted a pooled analysis of four clinical studies. These studies were selected as they are the large, pivotal, multi-site efficacy trials included in the DaTscan clinical development program. They were conducted to GCP standards in pre-defined populations, and were the ones submitted to support the NDA filing in the USA (3 of them for EU) for licensing. We did not include single site studies, small early development trials, or clinical utility studies in uncertain populations, because many of these had not evaluated DaTscan efficacy performance. Our intent was to use the original database from the NDA submission for the pooled analysis, and not to perform a meta-analysis of the published literature, because this has been done.[19, 20]

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METHODS

Participants

The research question was to determine the pooled diagnostic accuracy (sensitivity and specificity) of the four trials submitted to the US FDA application for ioflupane (^{123}I). [3, 13-15, 17] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN™ or DaTscan™ , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[21] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304 [also elsewhere sometimes known as PDT03004]). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Dates study was conducted	• Aug 1997 to Feb 1998	• Jan 1999 to Jun 2005	• Dec 2003 to Jun 2006	• Nov 2000 to Nov 2003

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[3, 13-15, 17] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection.

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Ioflupane (^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images.

Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all

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dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

In conducting the study, our goal was to evaluate the diagnostic accuracy of ioflupane (^{123}I) SPECT imaging using a large body of evidence. Our options were to perform a pooled analysis of data or a meta-analysis. We searched PubMed on October 4, 2013 using the terms (*FP-CIT or *Ioflupane[Title]) AND (Lewy or dementia or parkinson* or essential tremor[Title]) AND (diagnos* or accura*[Title]) and applied the filter "Human." The search retrieved 181 articles. After reviews, case reports, and commentaries were removed, 138 remained. Of these, 28 were clinical studies that evaluated the diagnostic accuracy of ioflupane (^{123}I),[3, 13-17, 22-44] with the number of subjects ranging from 16[38] to 326.[14] We selected four of these, which were the studies that were submitted to FDA to support the US NDA. These studies were the large, pivotal, multi-site efficacy trials conducted to GCP standards in pre-defined populations. We excluded single site studies, small early development trials, or clinical utility studies in uncertain populations, because many of these had not evaluated DaTscan sensitivity and specificity. We opted to perform a pooled analysis rather than a meta-analysis, because this had already been done.[19, 20] The first was performed in 2012 and summarized four studies with a total of 419 subjects with DLB. One of the studies included in this meta-analysis is the PDT301 study (with the baseline clinical evaluation) [3] included in our pooled analysis. This meta-analysis also showed high diagnostic accuracy, with sensitivity of 86.5% and specificity of 93.6%. The second was performed in 2007 and summarized 32 studies in subjects with parkinsonian syndromes, one of which was DP008-003.[13] The authors concluded that ioflupane (^{123}I) SPECT imaging was relatively accurate in differentiating early PD from normalcy, PD from ET, and PD from vascular parkinsonism.

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The current pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75·0% to 96·5%, and specificity ranged from 83·0% to 100·0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0·81 to 1·00, indicating that diagnostic accuracy is not dependent upon individual expert performance.

When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 15, 45] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies (PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003,

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enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[16, 21] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[16] Therefore, the use of clinical diagnosis as the non-perfect reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy,

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with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[46] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[24] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[47] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[48] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I) imaging results became available.[6, 49] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[50, 51] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[50] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

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Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[52] The Society of Nuclear Medicine,[53] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[54] the Scottish Intercollegiate Guidelines Network (SIGN),[55] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[56] Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[18, 57, 58] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[59] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA, DLB) and tauopathies (PSP, corticobasal degeneration).[60,61]

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Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies).

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

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WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

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Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

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Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

Data sharing statement

No additional data are available.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

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4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial. These four trials were selected because they were the four pivotal studies used for the US new drug application to the FDA.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD.

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Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

Abstract word count: 232

Funding: GE Healthcare (Princeton, NJ).

Keywords: Parkinson's disease, Movement disorders, Dementia, SPECT, Neuroradiology

Primary Subject Heading: Neurology

Secondary Subject Heading: Radiology and imaging

Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging indeed has high sensitivity and specificity for detecting the presence or absence of a striatal

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dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.

- Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis, particularly at follow-up after 12 months or later, is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration (FDA) approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. Numerous clinical trials have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[3, 13-18] However, each trial had limited numbers of subjects for whom results were available, ranging from 20 to 326.[3, 16] To better estimate the diagnostic performance of ioflupane (^{123}I), we conducted a pooled analysis of four clinical studies. These studies were selected as they are the large, pivotal, multi-site efficacy trials included in the DaTscan clinical development program. They were conducted to GCP standards in pre-defined populations, and were the ones submitted to support the NDA filing in the USA (3 of them for EU) for licensing. We did not include single site studies, small early development trials, or clinical utility studies in uncertain populations, because many of these had not evaluated DaTscan efficacy performance. Our intent was to use the original database from the NDA submission for the pooled analysis, and not to perform a meta-analysis of the published literature, because this has been done.[19, 20]

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METHODS

Participants

The research question was to determine the pooled diagnostic accuracy (sensitivity and specificity) of the four trials submitted to the US FDA application for ioflupane (^{123}I). ~~Four clinical trials were used for this pooled analysis, based on their similar designs and objectives; we used source data from studies performed in support of the ioflupane (^{123}I) US NDA.~~[3, 13-15, 17] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[21] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304 [also elsewhere sometimes known as PDT03004]). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Dates study was conducted	• Aug 1997 to Feb 1998	• Jan 1999 to Jun 2005	• Dec 2003 to Jun 2006	• Nov 2000 to Nov 2003

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[3, 13-15, 17] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection.

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Ioflupane (^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images.

Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all

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dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

In conducting the study, our goal was to evaluate the diagnostic accuracy of ioflupane (^{123}I) SPECT imaging using a large body of evidence. Our options were to perform a pooled analysis of data or a meta-analysis. We searched PubMed on October 4, 2013 using the terms (*FP-CIT or *Ioflupane[Title]) AND (Lewy or dementia or parkinson* or essential tremor[Title]) AND (diagnos* or accura*[Title]) and applied the filter "Human." The search retrieved 181 articles. After reviews, case reports, and commentaries were removed, 138 remained. Of these, 28 were clinical studies that evaluated the diagnostic accuracy of ioflupane (^{123}I),[3, 13-17, 22-44] with the number of subjects ranging from 16[38] to 326.[14] We selected four of these, which were the studies that were submitted to FDA to support the US NDA. These studies were the large, pivotal, multi-site efficacy trials conducted to GCP standards in pre-defined populations. We excluded single site studies, small early development trials, or clinical utility studies in uncertain populations, because many of these had not evaluated DaTscan sensitivity and specificity. We opted to perform a pooled analysis rather than a meta-analysis, because this had already been done.[19, 20] The first was performed in 2012 and summarized four studies with a total of 419 subjects with DLB. One of the studies included in this meta-analysis is the PDT301 study (with the baseline clinical evaluation) [3] included in our pooled analysis. This meta-analysis also showed high diagnostic accuracy, with sensitivity of 86.5% and specificity of 93.6%. The second was performed in 2007 and summarized 32 studies in subjects with parkinsonian syndromes, one of which was DP008-003.[13] The authors concluded that ioflupane (^{123}I) SPECT imaging was relatively accurate in differentiating early PD from normalcy, PD from ET, and PD from vascular parkinsonism.

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The current pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75·0% to 96·5%, and specificity ranged from 83·0% to 100·0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0·81 to 1·00, indicating that diagnostic accuracy is not dependent upon individual expert performance.

~~This pooled analysis of four clinical trials provides the largest set of clinical evidence to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, ioflupane (^{123}I) SPECT image evaluation demonstrated a sensitivity (ability to detect an SDDD when it is present) ranging from 75.0% to 96.5%, and a specificity (ability to exclude an SDDD when it is absent) ranging from 83.0% to 100.0%. Inter-reader agreement was high, indicating that diagnostic accuracy is not dependent upon individual expert performance.~~

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When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 15, 45~~22~~] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies (PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003, enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[16, 21] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[16] Therefore, the use of clinical diagnosis as the non-perfect

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reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy, with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[46~~23~~] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[24] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[47~~24~~] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[48~~25~~] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I)

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imaging results became available.[6, 49~~26~~] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[50~~27~~, 51~~28~~] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[50~~27~~] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[52~~29~~] The Society of Nuclear Medicine,[53~~30~~] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[54~~31~~] the Scottish Intercollegiate Guidelines Network (SIGN),[55~~32~~] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[56~~33~~]

Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on

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the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[18, 57~~34~~, 58~~35~~] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[59~~36~~] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA, DLB) and tauopathies (PSP, corticobasal degeneration).[60~~37~~,61~~38~~]

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Literature Review and Interpretation

We searched PubMed on October 4, 2013 using the terms (*FP-CIT or *Ioflupane[Title]) AND (Lewy or dementia or parkinson* or essential tremor[Title]) AND (diagnos* or accura*[Title]) and applied the filter "Human." The search retrieved 181 articles. After reviews, case reports, and commentaries were removed, 138 remained. Of these, 28 were clinical studies that evaluated the diagnostic accuracy of ioflupane (^{123}I),[3, 13-17, 39-61] with the number of subjects ranging from 16[55] to 326.[14] We selected four of these, which were the studies that supported the US NDA. We also found in our search two meta-analyses[19, 20] of the diagnostic accuracy of ioflupane (^{123}I) in DLB and parkinsonian syndromes. The first was performed in 2012 and summarized four studies with a total of 419 subjects. One of the studies included in this meta-analysis is the PDT301 study (with the baseline clinical evaluation)[3] included in our pooled analysis. The second was performed in 2007 and summarized 32 studies, one of which was DP008-003.[13]

This pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date of the diagnostic accuracy of ioflupane (^{123}I) SPECT imaging. The analysis includes patients with dementia and/or movement disorders. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75·0% to 96·5%, and specificity ranged from 83·0% to 100·0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0·81 to 1·00. Adoption and utilization of this new technology is expanding, reinforcing the usefulness of ioflupane (^{123}I) imaging as a validated diagnostic tool.

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Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies).

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

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WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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GE Healthcare provided funding and administrative support for this pooled analysis; managed statistical analysis, medical writing, and interpretation of the data; drafted sections of the manuscript; and reviewed, edited, and approved the manuscript.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

Dr. O'Brien reports grants and other from GE Healthcare, grants and other from Lilly, other from Bayer Healthcare, other from TauRx, other from Cytox, outside the submitted work.

Dr. Oertel reports grants and personal fees from GE Healthcare, personal fees from Amersham.Buchler, outside the submitted work.

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Dr. Sherwin reports other (salary) from GE Healthcare, during the conduct of the study; other (salary) from GE Healthcare, outside the submitted work.

Dr. Grachev reports employment from GE Healthcare, during the conduct of the study.

Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

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Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

Data sharing statement

Informed consent was not obtained from study participants for data sharing, but the presented data are anonymized and risk of identification is low. No additional data are available.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

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4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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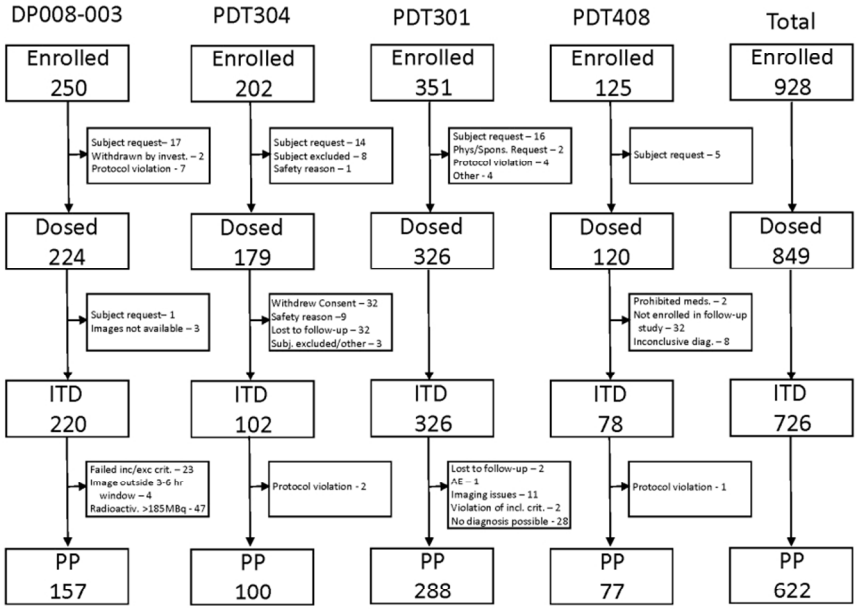

Note: Subjects may have more than one reason for discontinuing.

90x67mm (300 x 300 DPI)

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Fig. 2a

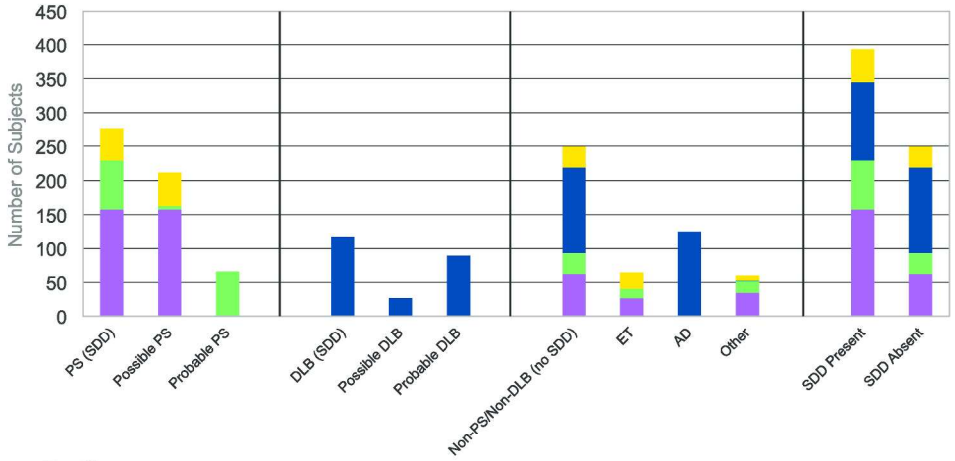
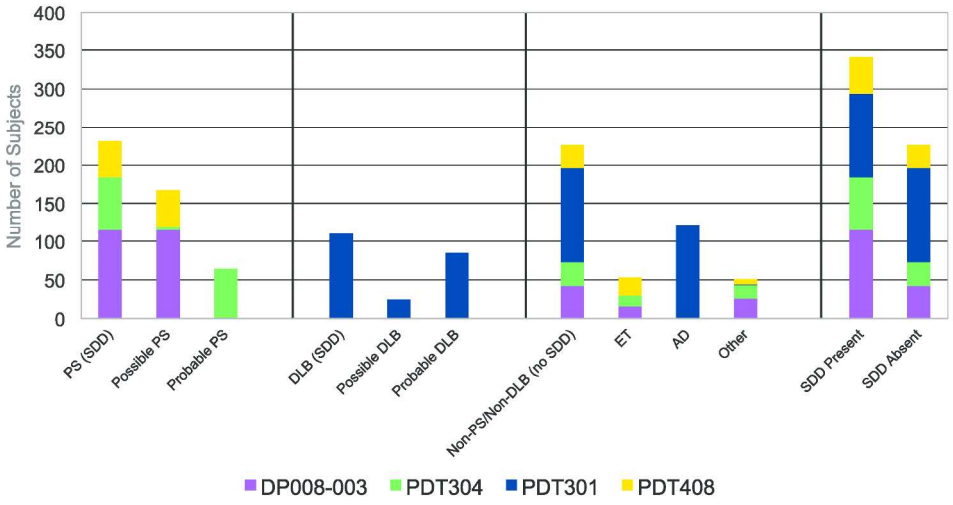


Fig. 2b



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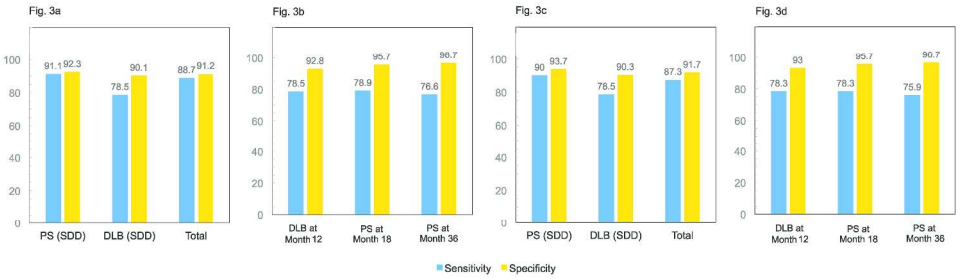

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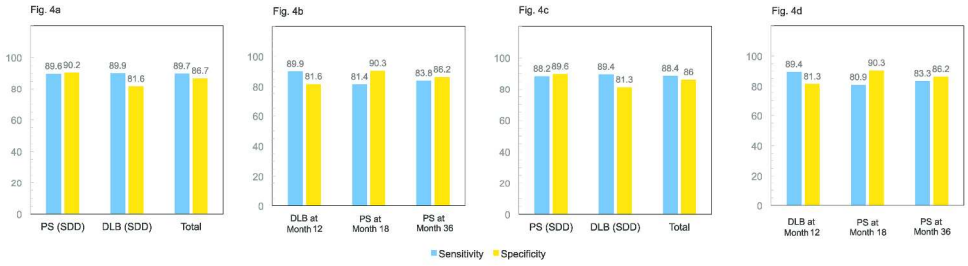

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Table S1. Investigators who participated in the four clinical trials in this pooled analysis.

DP008-003

Prof. EA van Royen, MD, PhD	AMC: University of Amsterdam Medical Centre (Academisch Medisch Centrum), Director of Department of Nuclear Medicine
Prof. Dr. WH Oertel	Chairman and Professor of Neurology, Department of Neurology, Klinikum, Philipps-University, Marburg, Germany
Prof. Dr. K Joseph	[Klinisch orientierte Tätigkeit auf dem Gesamtgebeit der Nuklearmedizin: 192 wissenschaftliche Veröffentlichungen]
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Dr. A Storch	University of Ulm, Department of Neurology, Oberer Eselsberg 45, 89081 ULM, Germany
Dr. V Ries	Tätigkeit als Arzt im Praktikum an der Neurologischen Universitätklinik Ulm
Ms. A Gerstner	Tätigkeit als studentische Hilfskraft auf der internistisch/neurologischen Intensivstation des St. Josef-Hospitals Bochum
Ms. S Rura	Erstellung einer Doktorarbeit in der Arbeitsgruppe von Prof. Dr. W Oertel mit der Thematik Neuroprotektion im Parkinson-Tiermodell, Marburg
Dr. H Höffken (MD)	Abteilung fur Klinische Nuklearmedizin, Zentrum Radiologie des Klinkums der Phippsuniversität Marburg, Baldingerstraβe, 35033 Marburg
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Dr. MWIM Horstink (MD, PhD)	University of Nijmegen
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Dr. J Versijpt	Hoekskensstraat 130, 9080 Lochristie (getting PhD w/ Dr. Dierckx)
Dr. A Van den Eeckhaut	Essestraat 83, 9340 Lede (w/ Dr. Dierckx)
Dr. AJ Lees (MB BS, MRCP [UK], MD, FRCP)	Consultant Neurologist to the National Hospital for Neurology and Neurosurgery and University College London Hospitals….

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Prof. Dr. Lars-Olof Wahlund	Karolinska Universitetssjukhuset, Huddinge, Hälsovägen, Flemingsberg, 14186 Stockholm, Sweden
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Table S2. Ethics Committees for the Four Studies in the Pooled Analysis

Study DP008-003

Committee Name	City	Country	Chairman
Medical Research Ethics Committee, The Phillips University Clinic	Marburg	Germany	Dr. P Heubel
The Faculty of Medicine Ethics Committee, Ludwig Maximilian University of Munich	Munich	Germany	Prof. Dr. med. Dent. W Gernet
Southern General Hospital Medical Ethics Committee	Glasgow	UK	Rev. D Keddie
Medical Ethics Committee, Academic Medical Center, Amsterdam University	Amsterdam	The Netherlands	Prof. L Arisz
Joint UCL/UCLH Committees on the Ethics of Human Research	London	UK	Prof. A McLean
Ethics Review Committee, University Hospital	Ghent	Belgium	Prof. Dr. M Bogaert

PDT301

Committee Name	City	Country	Chairman
Ethikkommission des Landes Oberösterreich	Linz	Austria	Univ. Prof. Prim Dr. Fisher
Ethik-Kommission der Medizinischen Fakultät der Universität Wien und des Allgemeinen Krnkenhauses der Stadt Wien AKH	Wien	Austria	Univ. Prof. Dr. E Singer
Comité consultative pour la protection des personnes dans la recherché biomédicale Bordeaux B	Bordeaux	France	Prof. MC Saux
Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig	Leipzig	Germany	Prof. Dr. med. R Preiß
Ethikkommission, Campus Charité Mitte	Berlin	Germany	Prof. Dr. med. R Uebelhack
Ethik-Kommission der Ruhr- Universität Bochum, Medizinischen Fakultät	Bochum	Germany	Prof. Dr. Zenz
Ethik-Kommission der Georg-August-Ruhr-Universität Göttingen	Göttingen	Germany	Prof. Dr. med. E Rüther
Ethik-Kommission der Ärztekammer Hamburg	Hamburg	Germany	Prof. Dr. med. Th. Weber
Medizinischen Hochschule Hannover, Ethikkommission	Hannover	Germany	Prof. Dr. HD Tröger
Landesärztekammer Rheinland-Pfalz, Ethikkommission	Mainz	Germany	Prof. Dr. Rittner

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Committee Name	City	Country	Chairman
Kommission für Ethik in der ärztlichen Forschung. Bereich Humanmedizin, Klinikum der Philipps- Universität Marburg	Marburg	Germany	Prof. Dr. Med. G Richter
Regione Veneto, Aziendo Ospedaliera di Padova, Comitato Etico per la Sperimentazione	Padova	Italy	Dr. R Pegoraro
Azienda Ospedaliera Pisana, Comitato etico per la studio del farmaco sull' uomo	Pisa	Italy	Prof. R Barsotti
Regional komité for medisinsk forskninsetikk, Vest-Norge (REK Vest), Universitetet i Bergen, det medisinske fakultet	Bergen	Norway	A Berstad
Comité Ético de Investigação Clinica	Porto	Portugal	
Karolinska Institutet, Forskningsettikkommitté Syd	Stockholm	Sweden	Prof. H Glaumann
Regionala etikprövningsnämnden i Stockholm	Stockholm	Sweden	Prof. LE Rutquist
Clinic Barcelona, Hospital Universitari, Comitè ètic investigaciò clinica	Barcelona	Spain	
Comité Etico de Investigación Clinica, Hospital Universitario de Getafe	Madrid	Spain	
Comité etico de investigación clinica Hospital "La Fe" Valencia	Valencia	Spain	
Northern and Yorkshire Multi-Centre Ethics Committee, Durham University	Durham	UK	J Kelly/S Brunton-Shiels
Gateshead Local research Ethics Committee	Sunderland	UK	Dr. DG Raw
Northumberland, Tyne and Wear NHS Strategic Health Authority Local Research Ethics Committees, Newcastle General Hospital	Newcastle upon Tyne	UK	Dr. J Lothian, PD Carr
Southampton & South West Hampshire Local Research Ethics Committee	Southampton	UK	C Wright
Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilans-Universität, LMU, Klinikum Großhadern	München	Germany	Prof. Dr. G Paumgartner
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig
Aligemeines öffentliches Krankenhaus der Stadt Linz, Kommission zur Beurteilung klinischer Prüfungen von Arzneimitteln, Ethikkommission	Linz	Austria	Primar Dr. H Stekel
Ospedali Civili Brescia, Aziendo Ospedaliera, Comitato Etico	Brescia	Italy	Prof. F De Ferrari

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Committee Name	City	Country	Chairman
Fakultní nemocnice v Motole, Etickákomise	Prague	Czech Republic	MUDr. V Šmelhaus
Brighton and Sussex Local Research Ethics Committee	Brighton	UK	Dr. P Seddon
East Sussex Local Research Ethics Committee	Brighton	UK	Dr. J Rademaker
South Manchester Local Research Ethics Committee	Manchester	UK	Dr. W Pettit
Central Manchester Research Ethics Committee	Manchester	UK	Dr. D Mandal
NHS Tayside Board, Tayside Committee on Medical Research Ethics, Ninewells Hospital & Medical School	Dundee	UK	NF Brown
Fazio-Fondazione San Raffaele Del Monte Tabor Milano, Comitato Etico Dell'istituto Nazionale Neurologico Besta di Milano	Milano	Italy	Prof. E Müller
IRCCS – Fondazione San Raffaele Del Monte Tabor di Milano	Milano	Italy	Prof. G Zoppei
Comité ético de investigación clínica, Servicio Andaluz de Salud, Consejería de Salud, Hospitales Universitarios Virgen de Rocío de Sevilla	Sevilla	Spain	
Ethikkommission der stadt Wien	Wien	Austria	Dr. H Serban
North Sheffield Local Research Ethics Committee, Northern General Hospital	Sheffield	UK	Dr. G PM Clark
Glasgow West Local Research Ethics Committee	Glasgow	UK	Dr. J Hunter
NHS Greater Glasgow Primary Care Division Local Research Ethics Committee, Gartnavel Royal Hospital	Glasgow	UK	Dr. P Fleming
Frenchay Research Ethics Committee, North Bristol NHS Trust Headquarters	Bristol	UK	Drs. Kendall and M Shere
Ärztekammer Berlin, Ethik-Kommission	Berlin	Germany	C Biondo
Ethikkommission des Landes Bremen, Institut für Klinische Pharmaakologie, Klinikum Bremen-Mitte	Bremen	Germany	Dr. K Boomgaarden-Brandes
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig

PDT304

Committee Name	City	Country	Chairman
Ethics Committee of the Southern General Hospital NHS Trust, Glasgow	Glasgow	UK	Rev. D Keddie

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Committee Name	City	Country	Chairman
Kommission für Ethik in der Ärztlichen Forschung, Klinikum der Philipps-Universität Marburg	Marburg	Germany	Prof. Dr. med. G Richter
New Cross Hospital Local Research Ethics Committee	Wolverhampton	UK	D.S.Little
Southampton and South West Hampshire Joint Local	Southampton	UK	Dr. A Kermode
Joint Ethics Committee Newcastle and North Tyneside Health Authority	Newcastle	UK	Prof. PA Heasman
Comite Etico de Investigacion Clinica Hospital Clinic I Provincial	Barcelona	Spain	Prof. J Rodes
Comite Etico de Investigacion Clinica del Hospital de la Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrenca
Comité d' éthique hospitalier, Cliniques Universitaires de Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Hospitais da Universidade de Coimbra	Coimbra	Portugal	Dr. JA Branquinho de Carvalho
Ethikkommission der Medizinischen Faultät der Universität Innsbruck	Innsbruck	Austria	Univ. Prof. Dr. P Lukas

PDT408

Committee Name	City	Country	Chairman
Hospital Ethical Committee, University Hospital UCL Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Commission for Ethics, AZ St.-Jan AV	Brugge	Belgium	Dr. J Van Droogenbroeck
Comite Consultatif de Protection des Personnes Dans La Recherche Biomedicale de Lille, Hôpital Huriez	Lille	France	Prof. PY Hatron
Ethik-Kommission der Ärztekammer Hamburg Kōrperschaft des ōffentlichen Rechts	Hamburg	Germany	Prof. Dr. Med. K Held
Ethikkomission des Klinikums der Universität Regensberg	Regensberg	Germany	Prof. Dr. R Andreesen
Vorsitzenden der Ethikkommission Bei der Ärztekammer des Saarlandes	Saarbrücken	Germany	Dr. S Ertz
Spett. Le Comitato Etico	Milano	Italy	Prof. A Randazzo
Comitato Etico Per La Sperimentazione Clinica Del Farmaci	Firenze	Italy	Prof. L Zilletti

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Committee Name	City	Country	Chairman
Ministério Da Saúde Hospitais Da Universidade De Coimbra	Coimbra	Portugal	Prof. Dr. JM Pedroso Lima
Comité Ético De Investigación Clínica Hospital Clínic I Provincial	Barcelona	Spain	Prof. MA Asenjo Sebastián
Comité Ético De Investigación Clínica Del Hospital De La Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrencá
King's College Hospital	London	UK	Prof. ER Howard
Southampton and South West Hampshire Local Research Ethics Committees	Southampton	UK	Dr. A Kermode
Etik-Kommission Der Medizinischen Faultät der Universität Wien	Wien	Austria	Univ. Prof. Dr. E Singer

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Table S3. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – PP population (N = 622)

		Study				
		DP008-003 (N = 157)	**PDT304 (N = 100)**	**PDT301 (N = 288)**	**PDT408 (N=77)**	**Total (N = 622)**
Age (yr)	Mean (SD)	63.1 (8.51)	60.5 (10.97)	74.2 (7.02)	64.1 (12.05)	67.9 (10.61)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	64.0	61.5	75.0	67.0	69.0
Gender	Male	99 (63%)	57 (57%)	160 (56%)	40 (52%)	356 (57%)
	Female	58 (37%)	43 (43%)	128 (44%)	37 (48%)	266 (43%)
Race	Caucasian	153 (97%)	100 (100%)	288 (100%)	76 (99%)	617 (99%)
	Black	3 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		115 (73%)	69 (69%)	0 (0%)	47 (61%)	231 (37%)
Possible PS		115 (73%)	5 (5%)	0 (0%)	47 (61%)	167 (27%)
Probable PS		0 (0%)	64 (64%)	0 (0%)	0 (0%)	64 (10%)
DLB (SDDD)		0 (0%)	0 (0%)	110 (38%)	0 (0%)	110 (18%)
Possible DLB		0 (0%)	0 (0%)	25 (9%)	0 (0%)	25 (4%)
Probable DLB		0 (0%)	0 (0%)	85 (30%)	0 (0%)	85 (14%)
Non-PS/Non-DLB (no SDDD)		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)
ET		16 (10%)	14 (14%)	0 (0%)	23 (30%)	53 (9%)
AD		0 (0%)	0 (0%)	122 (42%)	0 (0%)	122 (20%)
Other		26 (17%)	17 (17%)	1 (<1%)	7 (9%)	51 (8%)
SDDD Present[a]		115 (73%)	69 (69%)	110 (38%)	47 (61%)	341 (55%)
SDDD Absent		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; ET = Essential tremor; N = number of subjects in the study; PP = Per protocol; PS = Parkinsonian syndrome; SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Table S4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[a] – Baseline	91.1% (89.2 to 92.8)	92.3% (89.3 to 94.7)	78.5% (72.7 to 83.5)	90.1% (86.8 to 92.8)	88.7% (86.8 to 90.4)	91.2% (89.0 to 93.0)
Mean Results Across all Readers[b] – Month 12			78.5% (72.7 to 83.5)	92.8% (89.6 to 95.2)		
Mean Results Across all Readers[c] – Month 18	78.9% (72.8 to 84.2)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	76.6% (70.1 to 82.3)	96.7% (90.6 to 99.3)				

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Summary results calculated across all studies and readers at baseline.

[b] Summary results calculated across all readers for study PDT301.

[c] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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Table S5. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[a] – Baseline	90.0% (87.6 to 92.0)	93.7% (90.4 to 96.2)	78.5% (72.7 to 83.5)	90.3% (87.0 to 93.0)	87.3% (85.1 to 89.3)	91.7% (89.5 to 93.7)
Mean Results Across all Readers[b] – Month 12			78.3% (72.5 to 83.4)	93.0% (89.8 to 95.4)		
Mean Results Across all Readers[c] – Month 18	78.3% (72.0 to 83.7)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	75.9% (69.3 to 81.7)	96.7% (90.6 to 99.3)				

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Summary results calculated across all studies and readers at baseline.

[b] Summary results calculated across all readers for study PDT301.

[c] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-4
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	7
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	8-12, Table 1[a]
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	8-12[a]
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	8-13[a]
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	8-13[a]
Test methods	7	The reference standard and its rationale.	12-13, 24-25
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	12-13
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	12-13
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	8-13[a]
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	12-13
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	13-14
	13	Methods for calculating test reproducibility, if done.	14
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	7[a]
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Tables 1, 2, & S3
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	Figure 1
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	13
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Figure 2
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A[a]
	20	Any adverse events from performing the index tests or the reference standard.	N/A[b]
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Figs 3 & 4, Tables 3, 4, S4, & S5
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A[a]
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	23, Tables 3, 4, S4, & S5

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	24	Estimates of test reproducibility, if done.	23
DISCUSSION	25	Discuss the clinical applicability of the study findings.	24-27

[a] Since this was a pooled analysis of 4 clinical trials and each of these individual studies have been previously published, some of these details are not included in this paper with the references provided. The individual primary publications of the 4 studies were referred to to obtain these details.
[b] Safety data were not a focus of the current report and will be published in a separate report.

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial. These four trials were selected because they were the four studies used for the US new drug application to the FDA.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD. Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

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Funding: GE Healthcare (Princeton, NJ).

Keywords: Parkinson's disease, Movement disorders, Dementia, SPECT, Neuroradiology

Primary Subject Heading: Neurology

Secondary Subject Heading: Radiology and imaging

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Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.

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- Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis, particularly at follow-up after 12 months or later, is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration (FDA) approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. We searched the literature and found numerous clinical trials that have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[13-43] However, each trial had limited numbers of subjects for whom results were available, ranging from 16 to 326.[37, 15] Our search revealed that two meta-analyses have been performed evaluating diagnostic accuracy of SPECT imaging in DLB and in parkinsonian syndromes.[44,45] However, no previous pooled data analysis had been undertaken and the aim of this study was to undertake a pooled analysis using the four clinical studiesthat were the large, multi-site efficacy trials submitted to support the new drug application (NDA) filing in the USA (3 of them for EU) for licensing. They were conducted to good clinical practice (GCP) standards in pre-defined populations. Meta-analyses do not allow combination of individual subject's data; only mean values from each study publication are used, rather than maximizing information from the raw data. Meta-analyses include all available studies, and may include small, exploratory, non-GCP studies; and may include tracer prototypes (e.g., non-approved tracers such as B-CIT)

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that are not manufactured to commercial tracer quality, with robust, regulatory-accepted good manufacturing practice (GMP) processes.

Although two of our studies had been included in each of the meta-analyses (PDT301 baseline [14] in [44], and DP008-003 [13] in [45]), the other two had not. Performing a pooled analysis would provide a large body of evidence on the diagnostic performance of ioflupane (^{123}I) in subjects with movement disorders or dementia.

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METHODS

Participants

The research question was to determine the pooled diagnostic accuracy (sensitivity and specificity) of the four trials submitted to the US FDA application for ioflupane (^{123}I).[13-18] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy-3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN™ or DaTscan™ , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[46] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304 [also elsewhere sometimes known as PDT03004]). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Dates study was conducted	• Aug 1997 to Feb 1998	• Jan 1999 to Jun 2005	• Dec 2003 to Jun 2006	• Nov 2000 to Nov 2003

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[13-18] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection. Ioflupane

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(^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images. Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis

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assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

The current pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75.0% to 96.5%, and specificity ranged from 83.0% to 100.0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0.81 to 1.00, indicating that diagnostic accuracy is not dependent upon individual expert performance.

When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 16, 47] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies

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(PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003, enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[19, 46] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[19] Therefore, the use of clinical diagnosis as the non-perfect reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

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Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy, with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[48] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[23] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[49] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[50] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I) imaging results became available.[6, 51] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[52, 53] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[52] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in

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DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[54] The Society of Nuclear Medicine,[55] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[56] the Scottish Intercollegiate Guidelines Network (SIGN),[57] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[58] Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[20, 59, 60] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[61] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA,

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DLB) and tauopathies (PSP, corticobasal degeneration).[62,63]

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Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies), as well as contributing to the interpretation of the data in this pooled analysis.

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript, as well as contributing to the analysis and interpretation of this pooled analysis.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

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JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

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Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

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Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

Data sharing statement

No additional data are available.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

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4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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Is Ioflupane I123 Injection Diagnostically Effective in Patients with Movement Disorders and Dementia? Pooled Analysis of Four Clinical Trials

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Abstract

Objectives: To pool clinical trials of similar design to assess overall sensitivity and specificity of Ioflupane I 123 Injection (DaTSCAN™ or ioflupane (^{123}I)) to detect or exclude a striatal dopaminergic deficit disorder (SDDD), such as Parkinsonian syndrome and dementia with Lewy bodies.

Design: Pooled analysis of three Phase 3 and one Phase 4 clinical trial. These four trials were selected because they were the four studies used for the US new drug application to the FDA.

Setting: Multi-center, open-label, non-randomized.

Participants: Patients with either a movement disorder or dementia, and healthy volunteers.

Interventions: Ioflupane (^{123}I) was administered.

Outcome measures: Images were assessed by panels of 3-5 blinded experts and/or on-site nuclear medicine physicians, classified as normal or abnormal, and compared with clinical diagnosis (reference standard) to determine sensitivity and specificity.

Results: Pooling the four studies, 928 subjects were enrolled, 849 were dosed, and 764 completed their study. Across all studies, when images were assessed by on-site readers, ioflupane (^{123}I) diagnostic effectiveness had an overall (95% CI) sensitivity of 91.9% (88.7 to 94.5) and specificity of 83.6% (78.7 to 87.9). When reads were conducted blindly by a panel of independent experts, the overall sensitivity was 88.7% (86.8 to 90.4) and specificity was 91.2% (89.0 to 93.0).

Conclusions: In this pooled analysis, the visual assessment of ioflupane (^{123}I) images provided high levels of sensitivity and specificity in detecting the presence/absence of an SDDD. Ioflupane (^{123}I) imaging has the potential to improve diagnostic accuracy in patients with signs and symptoms of a movement disorder and/or dementia.

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Funding: GE Healthcare (Princeton, NJ).

Keywords: Parkinson's disease, Movement disorders, Dementia, SPECT, Neuroradiology

Primary Subject Heading: Neurology

Secondary Subject Heading: Radiology and imaging

Article Summary

Article focus

- The ability to visualize striatal dopamine transporter *in vivo* has enhanced clinicians' ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not.
- Several clinical trials with limited numbers of subjects have been performed to provide some information about diagnostic value of ioflupane (^{123}I). However, some investigators still question the value ioflupane (^{123}I) provides for diagnosing movement disorders and dementia.

Strengths

- This study provides the largest and most definitive set of clinical evidence to date, summarizing experience from three Phase 3 and one Phase 4 trial with all data pooled for a new statistical analysis, N=726, showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in patients with movement disorders and dementia (Intent to diagnose (ITD) and Per protocol (PP) populations). Differences among different patient populations, and inter-reader blinded image evaluation results are reported.

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- Well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging, in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment.

Limitations:

- Studies did not have autopsy confirmation of diagnosis (found to be impractical for up to 36 months of follow-up in the majority of patients in early stage of the disease), though the standard of expert clinical diagnosis, particularly at follow-up after 12 months or later, is an accepted reference standard for biomarker validation studies.
- Only two of the studies (PDT301 and PDT304) used expert clinical panels to establish the clinical diagnosis; the others relied on on-site investigator diagnosis (though made blind to imaging findings, except one clinical utility study PDT408).

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INTRODUCTION

Despite the development of consensus clinical diagnostic criteria,[1-5] early and accurate diagnosis of common neurodegenerative conditions like Parkinson's disease (PD) and dementia with Lewy bodies (DLB) continues to present challenges. Delays in diagnosis cause unnecessary distress and uncertainty for subjects and their families, increase healthcare use through additional appointments and investigations, and increase the risk that patients will develop preventable disability.[6] Not surprisingly, the longer a patient is observed and the greater the amount of accumulated clinical information, such as response to medications and progression of signs and symptom, the greater the accuracy of the diagnosis.[7] Inaccurate diagnoses may result in prescription of inappropriate medications, needlessly exposing patients to potentially harmful side effects, while denying patients treatment of symptoms.[6] Furthermore, diagnostic discrimination between degenerative and non-degenerative diseases is important because disease course, therapy, and prognosis differ considerably among patients.[6, 8]

Differential diagnosis of movement disorders may be confounded by presence of inconsistent parkinsonian features and/or atypical presentation of classic symptoms. Differentiation of Alzheimer's disease (AD) from DLB is also difficult, even after multiple evaluations. Consensus clinical criteria[2-5, 9] without imaging results have good specificity (80%-90%), but sensitivity is highly variable and can be as low as 30%, with the most common misdiagnosis being AD.[9, 10]

The advent of *in vivo* visualization of striatal dopamine transporter using the radiopharmaceutical ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy- 3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN^{TM} or DaTscan^{TM} } and single-photon emission computed tomography (SPECT) imaging has enhanced clinicians'

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ability to differentiate diseases that involve loss of dopaminergic nigrostriatal neurons from those that do not. Throughout this paper, we will refer to these disorders as striatal dopaminergic deficit disorders (SDDD), which is the clinico-patho-anatomical term used here as a group term for the clinical reference diagnoses of Parkinsonian syndrome (PS) and/or DLB, by virtue of them being recognized as clinical disorders that are known to have striatal dopaminergic deficit. Ioflupane (^{123}I) is the only approved imaging agent for this purpose; the European Medicines Agency (EMA) approved it under the trade name DaTSCAN™ (ioflupane (^{123}I) in 2000,[11] and the US Food and Drug Administration (FDA) approved it under the trade name DaTscan™ (Ioflupane I123 Injection) in 2011.[12] It is currently approved in 33 countries. We searched the literature and found numerous clinical trials that have been performed to establish the technical feasibility, and diagnostic effectiveness, sensitivity, and specificity of ioflupane (^{123}I).[13-43] However, each trial had limited numbers of subjects for whom results were available, ranging from 16 to 326.[37, 15] Our search revealed that two meta-analyses have been performed evaluating diagnostic accuracy of SPECT imaging in DLB and in parkinsonian syndromes.[44,45] However, no previous pooled data analysis had been undertaken and the aim of this study was to undertake a pooled analysis using the four clinical studiesthat were the large, multi-site efficacy trials submitted to support the new drug application (NDA) filing in the USA (3 of them for EU) for licensing. They were conducted to good clinical practice (GCP) standards in pre-defined populations. Meta-analyses do not allow combination of individual subject's data; only mean values from each study publication are used, rather than maximizing information from the raw data. Meta-analyses include all available studies, and may include small, exploratory, non-GCP studies; and may include tracer prototypes (e.g., non-approved tracers such as B-CIT)

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that are not manufactured to commercial tracer quality, with robust, regulatory-accepted good manufacturing practice (GMP) processes.

Although two of our studies had been included in each of the meta-analyses (PDT301 baseline [14] in [44], and DP008-003 [13] in [45]), the other two had not. Performing a pooled analysis would provide a large body of evidence on the diagnostic performance of ioflupane (^{123}I) in subjects with movement disorders or dementia.

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METHODS

Participants

The research question was to determine the pooled diagnostic accuracy (sensitivity and specificity) of the four trials submitted to the US FDA application for ioflupane (^{123}I).[13-18] All studies tested the effectiveness of ioflupane (^{123}I) {Iodine-123-fluoropropyl (FP)-carbomethoxy-3 β-(4-iodophenyltropane) (CIT) or Ioflupane I123 Injection or [^{123}I]Ioflupane or [^{123}I] FP-CIT or DaTSCAN™ or DaTscan™ , GE Healthcare, Amersham,UK. For the purposes of this report, ioflupane (^{123}I) will be used throughout the paper.} in detecting the loss of dopaminergic nigrostriatal neurons in subjects with symptoms and signs of movement disorders and/or dementia. The reference standard was the final clinical diagnosis of a disease that is known to have or not have a striatal dopaminergic deficit (hereafter called reference clinical diagnosis).[46] This clinical diagnosis was made blind to imaging results in three of the four studies (Phase 3 studies DP008-003, PDT301, PDT304 [also elsewhere sometimes known as PDT03004]). In two of the four studies (PDT301 and PDT304), the final clinical diagnosis was made by a panel of experts. Table 1 summarizes the attributes of the four studies. Although Phase 4 study PDT408 was designed to assess the clinical utility of ioflupane (^{123}I) image assessments as the primary endpoint, sensitivity and specificity were secondary endpoints, and the image results were included in the pooled analysis. The investigators who participated in each of the four studies are listed in Table S1 (supplementary table).

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Table 1 Summary of studies included in pooled analysis

	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Study design	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at baseline according to published consensus criteria as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Repeat-dose (max. of 3) • Expert clinical diagnosis at 36 months as the RCD	• Phase 3 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 12 months as the RCD	• Phase 4 • Multicenter, open-label, non-randomized • Single-dose • Expert clinical diagnosis at 24 months as the RCD
Dates study was conducted	• Aug 1997 to Feb 1998	• Jan 1999 to Jun 2005	• Dec 2003 to Jun 2006	• Nov 2000 to Nov 2003

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Population	• Healthy volunteers • Subjects with a clinical diagnosis of: ○ Parkinson's disease ○ Multiple system atrophy ○ Progressive supranuclear palsy, or ○ Essential tremor	• Healthy volunteers • Subjects with the clinical features of: ○ Early Parkinson's disease, or ○ Tremor (mainly essential tremor)	• Subjects with dementia (features of possible DLB or with features of other dementia [AD, VaD])	• Subjects with movement disorders (an uncertain clinical diagnosis as to PS or non-PS)

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Efficacy objectives	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary ○ Sensitivity and specificity for detecting or excluding an SDDD • Secondary ○ Inter-reader agreement	• Primary[a] ○ Impact of ioflupane (^{123}I) image assessments on patient diagnoses, confidence that patient had PS, and planned management • Secondary ○ Sensitivity and specificity for detecting or excluding an SDDD
Type of control	No control used	No control used	No control used	No control used
Investigational product	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 3 doses 18 months apart	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose	Ioflupane (^{123}I) 111-185 MBq (3 to 5 mCi) iv, 1 dose (73 subjects) or 2 doses 24 months apart (14 subjects)
No. of study centers	6	10	40	15
No. of subjects enrolled	250	202	351	125

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	Principal Study			
	DP008-003	**PDT304**	**PDT301**	**PDT408**
Age of ITD population, range (mean)	40, 80 (62.7)	33, 79 (60.4)	54, 90 (73.9)	25, 84 (64.2)
Gender	62% male, 38% female	56% male, 44% female	57% male, 43% female	58% male, 42% female
Race	Caucasian 98% Black 1% Asian <1%	Caucasian 100%	Caucasian 100%	Caucasian 99% Asian 1%
No. of subjects evaluable for efficacy	220	102	288	118
Blinded reads performed	Yes	Yes	Yes	No

AD = Alzheimer's disease; DLB = dementia with Lewy bodies; ITD = intent to diagnose; MBq = megabecquerel; PS = Parkinsonian syndrome; RCD = reference clinical diagnosis; SDDD = striatal dominergic deficit disorder; VaD = vascular dementia.

[a] Primary objective was to assess clinical utility of ioflupane (^{123}I) images, however, images were used for pooled efficacy analysis.

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All studies were conducted in accordance with the current revision of the Declaration of Helsinki; the Good Clinical Practice: Consolidated Guideline, approved by the International Conference on Harmonisation; and applicable national and local laws. Ethics Committees or Institutional Review Boards approved the protocol and amendments for each study (See Supplementary Table S2). Subjects or their guardians gave written informed consent after the aims, methods, anticipated benefits, and potential hazards were explained, and prior to commencing any study procedures or assessments. The informed consent for each study included a provision for subsequent analyses, of which this pooled analysis is an example. Study PDT301 is identified in clinicaltrials.gov as NCT00209456. All other trials began enrolling prior to 01 July 2005, the cut-off date for the initiation of the requirement by the International Committee of Medical Journal Editors for trials to be registered, so are not associated with any public database identifiers.

Procedures

All studies, including each study's inclusion and exclusion criteria, have been published;[13-18] a brief overview of the methods follows. All four studies were open-label, non-randomized, Phase 3 or 4 clinical trials to determine the sensitivity (positive percent agreement [PPA]) and specificity (negative percent agreement [NPA]) of ioflupane (^{123}I) SPECT imaging to detect or exclude an SDDD in subjects with various movement disorders (PS, including PD, multiple system atrophy [MSA], and progressive supranuclear palsy [PSP]; or essential tremor [ET]), and/or dementia (DLB, AD, or vascular dementia [VaD]); and healthy volunteers. Subjects received either a single or repeat (up to three doses total) dose of 111-185 MBq of ioflupane (^{123}I). SPECT imaging was performed between three and six hours after injection. Ioflupane

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(^{123}I) images were read on-site (institutional reads), as well as by three or five independent blinded readers (blinded image evaluation, BIE) in three of the studies, and classified as normal (SDDD absent) or abnormal (SDDD present). Abnormal images were further classified as type 1, 2, or 3.[12] Expert clinical diagnosis using a blinded panel of three neurologists or dementia specialists established whether the subject had an SDDD (PD, PS, PSP, MSA, or DLB) or a non-SDDD (ET, AD, or VaD and healthy volunteers). Expert clinical diagnosis was established at various time points across the four studies: DP008-003 at baseline, PDT301 at baseline and Month 12, PDT408 at baseline and Month 24, and PDT304 at baseline, and Months 18 and 36. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images. Each ioflupane (^{123}I) image result was compared with the corresponding reference clinical diagnosis, and classified as a True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN) scan to allow calculation of sensitivity and specificity. Sensitivity was calculated as nTP / (nTP + nFN), (n = number of subjects). Specificity was calculated as nTN / (nTN + nFP).

Additional efficacy endpoints included inter-reader agreement between BIE readers, as well as BIE readers vs. on-site institutional readers (DP008-003, PDT304, and PDT301).

Statistical analysis

All statistical analyses were performed using Statistical Analysis Software (SAS Institute Inc., Cary, NC, USA). Demographic data were collected and are presented using descriptive statistics. Populations analyzed included *Enrolled* (all subjects who were enrolled in any one of the four studies), *Dosed* (all enrolled subjects who received ioflupane (^{123}I)), *Intent to diagnose* (ITD; all dosed subjects who underwent SPECT imaging and underwent the reference clinical diagnosis

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assessment for the relevant analysis), and *Per protocol* (PP; all subjects in the ITD population with no major protocol violations). Sensitivity and specificity were calculated for the ITD and PP populations, and are reported with 95% confidence intervals (CI). For the purpose of this report, we will be using sensitivity and specificity (equivalent to PPA and NPA). Pairwise inter-reader and BIE vs. on-site reader agreement were analyzed using Cohen's kappa statistic. Inter-reader agreement across all BIE readers was analyzed using Fleiss' kappa statistic.

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RESULTS

Subject disposition and characteristics

Subject disposition for each study and for the pooled analysis is shown in Figure 1. Of the 928 subjects enrolled, 849 (91%) were dosed, and 764 (82%) completed their study. The most common reasons for not completing a study included subject request/withdrew consent (85 subjects, 9%), lost to follow-up (34 subjects, 4%), and protocol violation (14 subjects, 2%). Eleven subjects (1%) did not complete due to safety concerns, including adverse events. Medical history data were not collected consistently across studies and could not be pooled for this analysis.

By-study and pooled subject baseline demographics are shown in Table 2 (ITD population; PP population in Supplementary Table S3). No meaningful differences were noted in baseline demographics between the ITD and PP populations. Age was similar in three of the four studies, with subjects in PDT301 being older—unsurprisingly because this study only included people with dementia. In all studies, there were more males than females, with a similar ratio across studies. The majority was Caucasian, with Blacks and/or Asians representing 1% or less in any single study. Clinical diagnoses represented in each study are tabulated in Tables 2 (ITD population) and S4 (PP population), and are presented graphically in Figures 2a (ITD population) and 2b (PP population). Overall, 393 (54%) of subjects in the ITD population were classified as having SDDD (SDDD present), while 249 (34%) were classified with conditions that did not have an SDDD (SDDD absent).

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Table 2. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – ITD population (N = 726)

		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
Age (yr)	Mean (SD)	62.7 (8.87)	60.4 (10.91)	73.9 (7.17)	64.2 (11.99)	67.6 (10.60)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	63.5	61.0	75.0	67.0	69.0
Gender	Male	136 (62%)	57 (56%)	187 (57%)	41 (53%)	421 (58%)
	Female	84 (38%)	45 (44%)	139 (43%)	37 (47%)	305 (42%)
Race	Caucasian	216 (98%)	102 (100%)	326 (100%)	77 (99%)	721 (99%)
	Black	3 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (<1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		158 (72%)	71 (70%)	0 (0%)	48 (62%)	277 (38%)
Possible PS		158 (72%)	5 (5%)	0 (0%)	48 (62%)	211 (29%)
Probable PS		0 (0%)	66 (65%)	0 (0%)	0 (0%)	66 (9%)

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		Study				
		DP008-003 (N = 220)	**PDT304 (N = 102)**	**PDT301 (N = 326)**	**PDT408 (N=78)**	**Total (N = 726)**
DLB (SDDD)		0 (0%)	0 (0%)	116 (36%)	0 (0%)	116 (16%)
Possible DLB		0 (0%)	0 (0%)	27 (8%)	0 (0%)	27 (4%)
Probable DLB		0 (0%)	0 (0%)	89 (27%)	0 (0%)	89 (12%)
Non-PS/Non-DLB (no SDDD)		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)
ET		27 (12%)	14 (14%)	0 (0%)	23 (29%)	64 (9%)
AD		0 (0%)	0 (0%)	125 (38%)	0 (0%)	125 (17%)
Other		35 (16%)	17 (17%)	1 (<1%)	7 (9%)	60 (8%)
SDDD Present[a]		158 (72%)	71 (70%)	116 (36%)	48 (62%)	393 (54%)
SDDD Absent		62 (28%)	31 (30%)	126 (39%)	30 (38%)	249 (34%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; BMI = Body mass index; DLB = Dementia with Lewy bodies; ET = Essential tremor; ITD = Intent to diagnose; N = number of subjects in the study; PS = Parkinsonian syndrome SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Sensitivity (PPA) and specificity (NPA)

Sensitivity and specificity for ioflupane (^{123}I) to detect SDDD (abnormal scan) or non-SDDD (normal scan) using the mean of BIE reads is displayed in Figure 3. Supplementary Tables S4 and S5 (ITD and PP populations, respectively) show the means and 95% CI for the individual reads for Parkinsonian syndromes, dementia with Lewy bodies, and total. Figure 3a shows high sensitivity and specificity in the ITD population for both movement disorders (PS) and the total pooled analysis, with a slightly lower sensitivity value (78.5%) when assessing subjects with dementia. Sensitivity and specificity did not change substantially when reference clinical diagnoses were made for DLB at Month 12. Sensitivity decreased when reference clinical diagnoses were made for PS at Months 18 and 36 (78.9% and 76.6%), but specificity values increased slightly, exceeding 95% at each time point. Overall, the sensitivity of BIE reads of ioflupane (^{123}I) SPECT images in the ITD population for PS and dementia at all diagnosis time points ranged from 76.6% to 91.1%, and specificity ranged from 90.1% to 96.7%; PP population results (Figs 3c and 3d) were very similar. Figures 4a-4d display the same analyses using the on-site read results. Overall, sensitivity in the ITD population (Fig 4a and 4b) ranged from 81.4% to 89.9%, and tended to be higher for on-site reads compared with the BIE reads. Specificity ranged from 81.6% to 90.3%, and tended to be lower compared with BIE reads. No meaningful differences were noted in the values when analyzing the PP population (Fig 4c and 4d). Tables 3 and 4 (ITD and PP populations, respectively) summarize the sensitivity and specificity by expert clinical diagnosis for on-site, institutional reads.

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Table 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – ITD population (N = 726)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	93.1% (89.5 to 95.8)	91.1% (84.6 to 95.5)	88.3% (80.0 to 94.0)	77.4% (69.7 to 83.9)	91.9% (88.7 to 94.5)	83.6% (78.7 to 87.9)
Study PDT301 – Month 12			89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)		
Study PDT304 – Month 18	81.4% (70.3 to 89.7)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.8% (72.9 to 91.6)	86.2% (68.3 to 96.1)				
Mean Results[b]	89.6% (86.3 to 92.4)	90.2% (84.9 to 94.1)	89.9% (81.7 to 95.3)	81.6% (73.7 to 88.0)	89.7% (86.7 to 92.2)	86.7% (82.4 to 90.3)

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site ioflupane (^{123}I) reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Table 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site institutional reads – PP population (N = 622)

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Pooled Studies[a]	91.8% (87.5 to 95.0)	90.3% (82.9 to 95.2)	87.5% (78.7 to 93.6)	77.1% (69.3 to 83.7)	90.6% (86.8 to 93.6)	82.6% (77.3 to 87.1)
Study PDT301 – Month 12			89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)		
Study PDT304 – Month 18	80.9% (69.5 to 89.4)	90.3% (74.2 to 98.0)				
Study PDT304 – Month 36	83.3% (72.1 to 91.4)	86.2% (68.3 to 96.1)				
Mean Results[b]	88.2% (84.5 to 91.3)	89.6% (83.8 to 93.8)	89.4% (80.8 to 95.0)	81.3% (73.3 to 87.8)	88.4% (85.1 to 91.2)	86.0% (81.4 to 89.8)

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a] Pooled studies include on-site [^{123}I]FP-CIT reads for DP008-003, PDT304, (at baseline), PDT301 (baseline reference clinical diagnosis), and PDT408.

[b] Summary results calculated across all studies and time points. For PDT301, the Month 12 reference clinical diagnosis was used. Sensitivity/Specificity for DLB is calculated based on Probable DLB vs. Non-DLB.

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Sensitivity/Specificity for Total is calculated based on SDDD vs. non-SDDD.

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Inter-reader agreement

Three of the studies had BIE readers, and Study PDT304 had three sets of images to be read. Overall, the agreement between the BIE reader pairs was good, and ranged from 0.81 (95% CI 0.73 to 0.90) to 1.00 (1.00 to 1.00). The Fleiss' kappa for all BIE readers in a study ranged from 0.88 (0.84 to 0.92) to 0.99 (0.87 to 1.10). Agreement between the BIE readers and the on-site read was similar for two of the studies, and ranged from 0.82 (0.73 to 0.90) to 0.94 (0.87 to 1.01); for Study PDT301, the agreement for this comparison was not as good, with kappa ranging from 0.60 (0.51 to 0.69) to 0.68 (0.60 to 0.76). Inter-reader agreement for the PP population was comparable to that determined for the ITD population (data not shown).

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DISCUSSION

The current pooled analysis provides the largest dataset of clinical evidence (N = 726 in the ITD population) to date showing that ioflupane (^{123}I) SPECT imaging has high sensitivity and specificity for detecting the presence or absence of a striatal dopaminergic deficit in ITD and PP population of patients with movement disorders and/or dementia. Another strength of this study is that we pooled well-designed, prospective studies with 12-36 months of clinical follow-up after ioflupane (^{123}I) imaging in which blinded image evaluation by 3-5 independent nuclear medicine physicians (no access to clinical information) was used for image assessment. Overall, sensitivity for detecting the presence or absence of an SDDD ranged from 75.0% to 96.5%, and specificity ranged from 83.0% to 100.0%. Inter-reader agreement was high, with kappa for blinded reader pairs ranging from 0.81 to 1.00, indicating that diagnostic accuracy is not dependent upon individual expert performance.

When BIE reads were compared with on-site reads, specificity was higher for the BIE reads, whereas sensitivity was higher for the on-site reads. BIE vs. on-site reader agreement was lower in the PDT301 study. This study focused on subjects with dementia, whereas the other studies focused primarily on subjects with movement disorders. Clinical diagnosis of DLB tends to be less accurate than PS.[10, 13, 16, 47] On-site readers had access to patient clinical information, whereas BIE readers did not. This likely contributed to the observed increase in sensitivity and decrease in specificity when images were read by the on-site readers compared with BIE readers, resulting in lower agreement between the two reader groups in this study.

A limitation of this study is that the four studies in the pooled analysis used expert clinical diagnosis as a reference standard for the presence or absence of an SDDD. Two of the studies

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(PDT301 and PDT304) used expert panels to establish the clinical diagnosis. In DP008-003, enrolled subjects had established diagnoses, so an expert panel was not considered necessary. In PDT408, the final diagnosis was made with access to the ioflupane (^{123}I) SPECT images, which was required to assess the test clinical utility. The truth standard for diagnosing movement disorders and dementia is neuropathological confirmation of brain tissue at autopsy. However, with a slowly progressive, mostly benign course of these disorders, these patients are unlikely to die during the course of relatively short clinical trial duration and be subjects for autopsy assessment. Previous post-mortem studies demonstrated a good correlation between ioflupane (^{123}I) SPECT imaging with neuropathological findings.[19, 46] In a study by Walker, when validation was by autopsy diagnosis, sensitivity and specificity of initial clinical diagnoses in DLB was 75% and 42%, respectively, whereas sensitivity and specificity of ioflupane (^{123}I) imaging was higher, with values of 88% and 83%, respectively (88% and 100% for semi quantitative analysis of scans).[19] Therefore, the use of clinical diagnosis as the non-perfect reference standard rather than neuropathological confirmation at autopsy may have contributed to the sensitivity and specificity values obtained in this pooled analysis. Another limitation of the study is that Study PDT408 was not designed specifically to assess the sensitivity and specificity of ioflupane (^{123}I) SPECT imaging for detecting or excluding an SDDD. However, they were secondary endpoints, and expert clinical diagnosis and ioflupane (^{123}I) images were available on these subjects, so it was deemed appropriate to include this study in the pooled analysis. Of note, the sensitivity and specificity values for this study fell within the range for the other three studies in which clinical diagnoses were made blinded to ioflupane (^{123}I) images, and exclusion of this study would not have altered the main findings reported here.

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Substantial clinical need has been established for an adjunct to existing diagnostic tools for differentiating PD from ET, and DLB from AD. Examiner expertise affects diagnostic accuracy, with sub-specialists having the highest accuracy, followed by general neurologists; primary care physicians tend to have the lowest.[48] In a general practice setting (N=202), 15% of patients who had been diagnosed with parkinsonism, had tremor with onset after the age of 50, or who had ever received parkinsonism drugs had their diagnosis unequivocally rejected when strict clinical diagnostic criteria were applied and they completed a detailed neurological interview.[23] On the other hand, 13 patients (19%) not previously diagnosed with Parkinson's disease (PD) received this diagnosis following use of strict clinical diagnostic criteria.[49] In another general practice setting in Scotland (N=610), 5% of patients taking antiparkinson therapy for a diagnosis of PD had their medication successfully withdrawn following evaluation by two movement disorder specialists; ioflupane (^{123}I) scanning was performed if there was uncertainty.[50] General neurologists changed the diagnosis in 75% and movement disorder specialists in 47% of clinically uncertain Parkinsonian Syndrome (PS) cases after ioflupane (^{123}I) imaging results became available.[6, 51] These studies highlight the frequency of PD or PS misdiagnosis, and illustrate how using ioflupane (^{123}I) scanning can result in corrections to treatment. Early diagnosis is confounded by the fact that these diseases are progressive, and it may take time for the signs and symptoms to worsen until they clearly point to one disease.[7] The choice of consensus criteria also affects the sensitivity and specificity of the clinical diagnosis.[52, 53] All these factors contribute to clinical diagnosis failing to align with autopsy findings up to 25% of the time.[52] Ioflupane (^{123}I) SPECT imaging does not diagnose disease. Rather, it is used to determine the presence or absence of a striatal dopaminergic deficit. The performance of ioflupane (^{123}I) reported here may have been lower than expected, particularly in

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DLB patients, because we were comparing it to clinical diagnosis based on consensus criteria, known to be imprecise.

Regulatory approval of ioflupane (^{123}I) in Europe and the US has facilitated meeting the clinical need to improve the accuracy of clinical diagnosis. Adoption and utilization of this new technology is expanding, and several professional societies and organizations are supporting ioflupane (^{123}I) imaging as a useful and validated diagnostic tool. These include mention in the 2013 EFNS/MDS-ES/ENS guideline (Category A),[54] The Society of Nuclear Medicine,[55] the UK's National Institute for Health and Clinical Excellence (NICE) 2006 guidance,[56] the Scottish Intercollegiate Guidelines Network (SIGN),[57] and the EFNS-ENS Guidelines.[4] The Parkinson Progression Marker Initiative (PPMI) is adding ioflupane (^{123}I) imaging to be included in study inclusion criteria, as well as during a 5-year study of PD biomarker progression.[58] Research is needed to more fully elucidate future applications of ioflupane (^{123}I) SPECT imaging. While not currently licensed for this application, discussions have recently focused on the possibility of whether quantitative analysis of ioflupane (^{123}I) binding might further increase the sensitivity and specificity of SDDD detection and enable differentiation of other PS, such as PSP, MSA, or vascular parkinsonism from PD.[20, 59, 60] Additional studies that compare ioflupane (^{123}I) imaging results with *post mortem* neuropathology rather than expert clinical diagnosis may document better the accuracy of estimates of sensitivity and specificity. Our use of expert clinical diagnosis as the standard of truth, whilst validated, was not as perfect as autopsy. In addition, not all DLB patients have nigrostriatal degeneration and a small percentage of these patients may have primarily cortical degeneration.[61] Finally, ioflupane (^{123}I) imaging may be helpful in identifying dopaminergic nigrostriatal degeneration in the prodromal stages, such as rapid-eye-movement sleep behavior disorder of alpha-synucleinopathies (PD, MSA,

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DLB) and tauopathies (PSP, corticobasal degeneration).[62,63]

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Contributors

JTO'B was a principal investigator responsible for design, conduct and aspects of data collection and supervision of the 301 study; he was involved in design and critical analysis of data forming this manuscript.

WHO contributed to the study designs, data collection, data analysis, and data interpretation.

IGMcK and ZW contributed to data collection.

DGG made substantial contribution to the acquisition, analysis and interpretation of the data.

KT was involved in the analysis and reporting of study results, which are presented in this manuscript (investigator and reader in part of the studies), as well as contributing to the interpretation of the data in this pooled analysis.

ET contributed to the study design, data analysis, and data interpretation.

PFS was involved in reporting of studies that resulted in data reported in this manuscript, as well as contributing to the analysis and interpretation of this pooled analysis.

IDG provided funding and administrative support; managed statistical analysis and medical writing; conducted literature search; interpreted the data; and drafted the first draft and efficacy sections of the manuscript.

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JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG reviewed and edited the manuscript, and approved the final version.

JTO'B, WHO, IGMcK, DGG, ZW, KT, ET, PFS, and IDG agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

JTO'B and IDG are guarantors of the study.

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GE Healthcare provided funding and administrative support for this pooled analysis~~.; managed statistical analysis, medical writing, and interpretation of the data; drafted sections of the manuscript; and reviewed, edited, and approved the manuscript.~~ All co-authors (except IDG and PFS, who were GE employees at the time the paper was prepared) contributed independent of the sponsor, as noted above, and retained full editorial control of the content and the decision to publish. No authors were paid for their participation in preparing this manuscript.

Competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that

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Dr. Sherwin reports other (salary) from GE Healthcare, during the conduct of the study; other (salary) from GE Healthcare, outside the submitted work.

Dr. Grachev reports employment from GE Healthcare, during the conduct of the study.

Researcher independence

All authors had full independence from the funding source in the conduct of the research reported in this paper (see competing interests).

Access to data

All authors, internal and external, had full access to all of the data, (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and accuracy of the data analysis.

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Transparency declaration

John T. O'Brien affirms that the manuscript is an honest, accurate, and transparent account of the study being reported. No important aspects of the study have been omitted. Any discrepancies from the study, as planned, have been explained.

Data sharing statement

Informed consent was not obtained from study participants for data sharing, but the presented data are anonymized and risk of identification is low. No additional data are available.

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Figure Legends

Figure 1. Subject disposition

Figure 2. Summary of clinical diagnosis (per Reference Clinical Standard) by study

Fig 2a. – ITD population

Fig 2b. – PP population

Figure 3. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Mean of Blind Reads

3a. ITD population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

3b. ITD population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

3c. PP population – Summary results calculated across all studies and readers at baseline. DLB is calculated based on Probably DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent

3d. PP population – DLB at Month 12 calculated for all readers in study PDT301. PS at Month 18 and 36 calculated for all readers in study PDT304.

Figure 4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – On-site Institutional Reads

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4a. ITD population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4b. ITD population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

4c. PP population – Summary results calculated across all studies and time points. For PDT301, Month 12 reference clinical diagnosis was used in this analysis. DLB is calculated based on Probable DLB vs. non-DLB. Total is calculated based on SDDD present vs. SDDD absent.

4d. PP population – DLB at Month 12 calculated for on-site readers in study PDT301. PS at Month 18 and 36 calculated for on-site readers in study PDT304.

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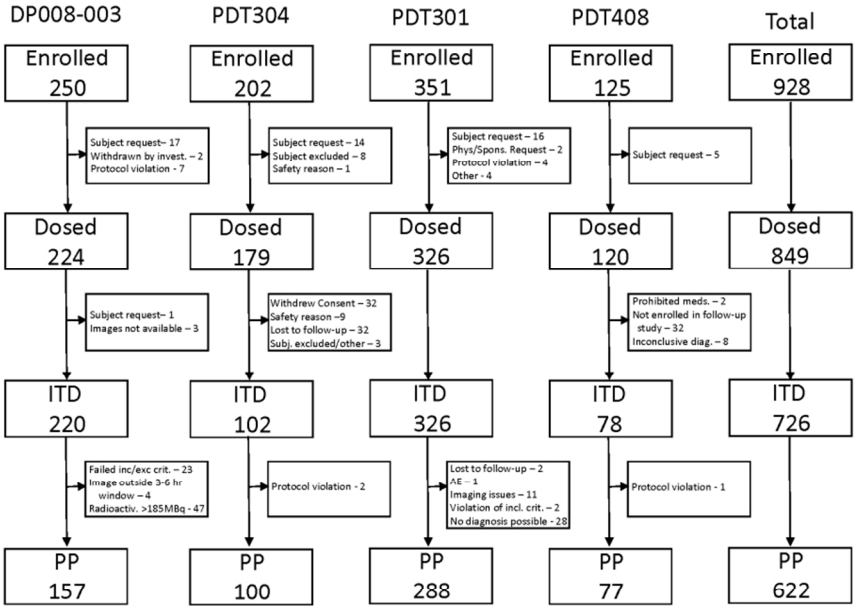

Note: Subjects may have more than one reason for discontinuing.

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Fig. 2a

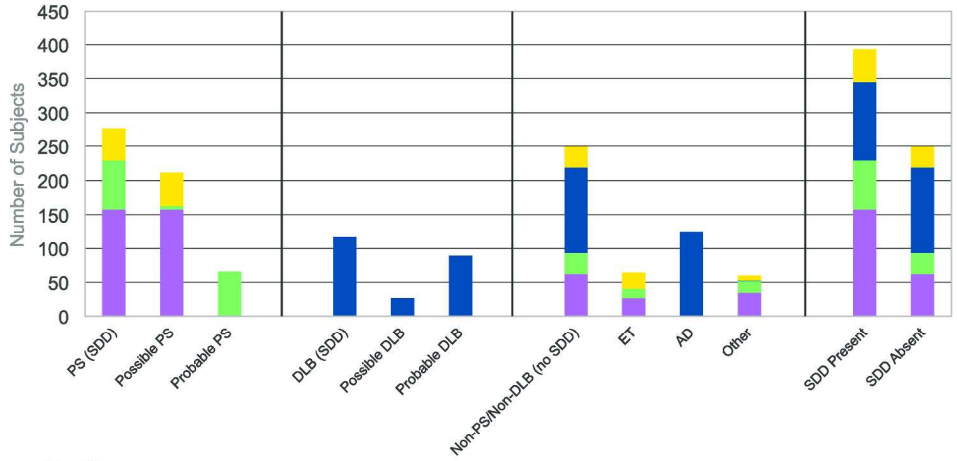
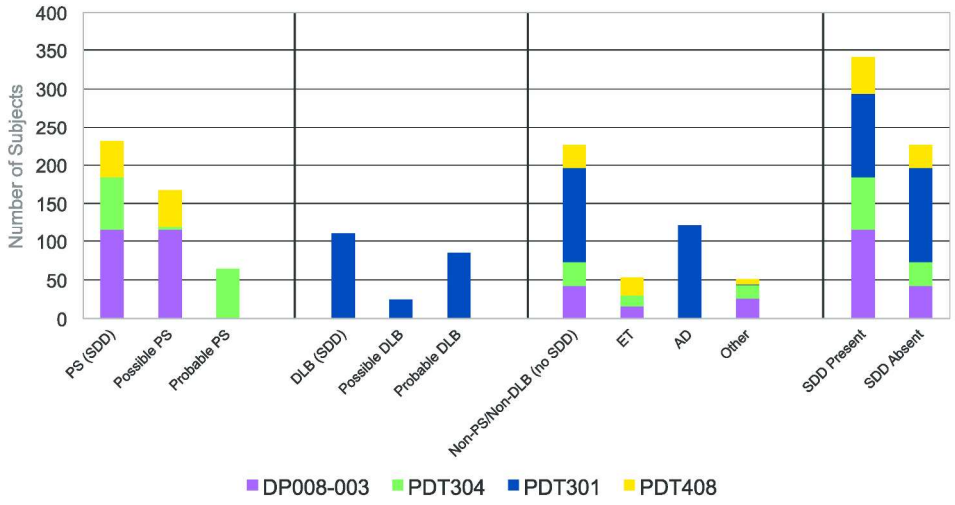


Fig. 2b



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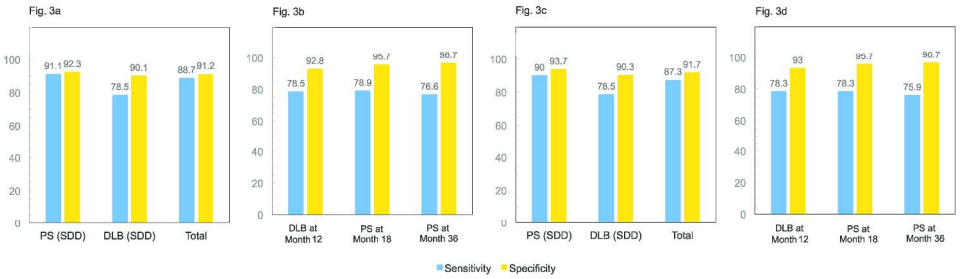

461x152mm (300 x 300 DPI)

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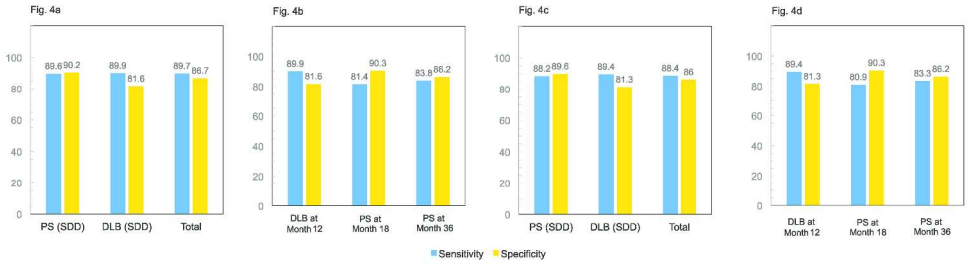

479x130mm (300 x 300 DPI)

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Table S1. Investigators who participated in the four clinical trials in this pooled analysis.

DP008-003	
Prof. EA van Royen, MD, PhD	AMC: University of Amsterdam Medical Centre (Academisch Medisch Centrum), Director of Department of Nuclear Medicine
Prof. Dr. WH Oertel	Chairman and Professor of Neurology, Department of Neurology, Klinikum, Philipps-University, Marburg, Germany
Prof. Dr. K Joseph	[Klinisch orientierte Tätigkeit auf dem Gesamtgebeit der Nuklearmedizin: 192 wissenschaftliche Veröffentlichungen]
Prof. Dr. K Tatsch	Department of Nuclear Medicine, Klinikum Grosshadern, University of Munich, Marchioninistr. 15, 81377, Munich, Germany
Dr. J Schwarz	Neurologische Klinik, Universität Ulm, 89081 Ulm
Dr. T Schwarzmüller, Dr. R Linke	University of Munich, Department of Nuclear Medicine, Klinikum Grosshadern, Marchioninistr. 15, 81377 Munich, Germany
Dr. A Storch	University of Ulm, Department of Neurology, Oberer Eselsberg 45, 89081 ULM, Germany
Dr. V Ries	Tätigkeit als Arzt im Praktikum an der Neurologischen Universitätklinik Ulm
Ms. A Gerstner	Tätigkeit als studentische Hilfskraft auf der internistisch/neurologischen Intensivstation des St. Josef-Hospitals Bochum
Ms. S Rura	Erstellung einer Doktorarbeit in der Arbeitsgruppe von Prof. Dr. W Oertel mit der Thematik Neuroprotektion im Parkinson-Tiermodell, Marburg
Dr. H Höffken (MD)	Abteilung fur Klinische Nuklearmedizin, Zentrum Radiologie des Klinkums der Phippsuniversität Marburg, Baldingerstraβe, 35033 Marburg
Dr. O Pogarell	Department of Neurology, University of Marburg, Rudolf-Biltmann-Str. 8, D-35033 Marburg, Germany
Dr. H Fritsch	Strahlenschutzbeauftragter der Abteilung für Klinische Nuklearmedizin, Steinweg 7, 35096 Weimar/Lahn
Dr. D Grosset (BSc, MD, FRCP)	Consultant Neurologist, Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, Govan Road, Glasgow, G51 4TF
Dr. J Patterson (BSc, PhD, MIPEM)	Principal Physicist, Department of Clinical Physics, Institute of Neurological Sciences, Southern General Hospital NHS Trust, Glasgow, G51 4TF and Honorary Research Assistant, University of Glasgow, Glasgow G12 8QQ Scotland
Dr. H Ben Amer (M.B B.ch, MRCP (UK)	
T Murphy RGN	Department of Neurology, Institute of Neurological Sciences, Southern General Hospital, 1345 Govan Road, Glasgow, GF1 4TF
Dr. JD Speelman	
Dr. MWIM Horstink (MD, PhD)	University of Nijmegen
Dr. J Booij	AMC, the Netherlands
Dr. J Versijpt	Hoekskensstraat 130, 9080 Lochristie (getting PhD w/ Dr. Dierckx)
Dr. A Van den Eeckhaut	Essestraat 83, 9340 Lede (w/ Dr. Dierckx)
Dr. AJ Lees (MB BS, MRCP [UK], MD, FRCP)	Consultant Neurologist to the National Hospital for Neurology and Neurosurgery and University College London Hospitals….

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Dr. DC Costa (MD, MSc, PhD, FRCR Dr. M Doder Dr. H Sips	Institute of Nuclear Medicine, University College London Medical School, Middlesex Hospital, Mortimer Street, London, W1N 8AA, UK
Prof. R Dierckx	Division of Nuclear Medicine, University Hospital Gent, De Pintelaan 185, B-9000 Gent, Belgium
Dr. D Decoo	UZ Gent, Dienst Neurologie, De Pintelaan 185, 9000-GENT
Dr. C Van Der Linden	Department of Neurology, University Hospital Gent, Gent, Belgium
Dr. Rhiannon Rowsell, Dr. R Robison, Mrs. B McDougall, Mrs. V Thody	Nycomed Amersham plc, White Lion Road, Little Chalfont, Buckinghamshire, HP7 9NA, UK
Dr. T Frear	Frear and Associates, 77 Benetfeld Road, Foxley Fields, Binfield, Berkshire, RG42 4EW, UK
Mrs. M Cobb	Nycomed Imaging, Clinical Research Associate, Nycomed Amersham plc, White Lion Road, Little Chalfont, Buckinghamshire, HP7 9NA, UK
Mrs. R Sakowski	General Manager/Clinical Trials Manager, Chiltern International GmbH, Ober-Eschbacher Straβe 91, 61352 Bgd Homburg v.d.H. Germany
Dr. C Deubelbeiss (PhD)	Clinical Research Associate, Chiltern International GmbH, Berner Str. 49, D-60437 Frankfurt, Germany
Dr. M Titulaer, Dr. M Al (MSc x 2, PhD)	Farma Research BV, Nijmegen (CRO), the Netherlands
HJW Adrianus (PhD?)	Als arts-assistant neurologie Radboudziekenhuis te Nijmegen
Svetislav Gacinovic (MsC, MD)	Institute of Nuclear Medicine, University College London Medical School, Mortimer Street, London, W1A 8AA, UK
PDT301	
Kendle GmbH & Co. GMI KG	Georg-Brauchle-Ring 6, 81929 München, Germany
Pharm-Olam International (UK) Ltd	The Brackens, London Road, Ascot, Berkshire, RG42 7UT, UK
Pharm-Olam International (UK) Ltd,	Jihovychodni VII, No. 11/928, 141 00 Prague 4, Zabehlice, Czech Republic
Phidea S.p.A.	Via C. Colombo 1, 20094 Corsico, Italy
Prof. Dr. Franz Aichner	OÖ Landesnervenklinik, Neurologische Abteilung, Wagner-Jauregg-Weg 15, 4020 Linz, Austria
Prof. Dr. Susanne Asenbaum	Universitätshospital Wien, Abteilung Neurologie, Währinger Gürtel 18-20a, 1090 Wien, Austria
Prof. Dr. Jean M. Orgogozo	Université Bordeaux, Hôpital Pellegrin, Place Amélie Raba Léon, 33076 Bordeaux, France
Prof. Dr. Florence Pasquier	Hôpital Roger Salengro, Rue Prof Emile Laine, 59000 Lille, France

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Prof. Dr. Johannes Schwarz	Klinik und Poliklinik für Neurologie, Universitätsklinikum Leipzig, Liebigstr. 22a, 04103 Leipzig, Germany
Dr. Guy Arnold, PD Dr., Eike Spruth, PD Dr.	Humbold-Universität Berlin, Medizinische Fakultät Charité Mitte, Abteilung Neurologie, Schumannstr. 21, 10117 Berlin, Germany
Dr. Prof. Thomas Müller	St. Josef-Hospital, Ruhr-Universität Bochum, Gudrunstr. 56, 44791 Bochum, Germany
Dr. Inga Zerr	Georg-August Universität Göttingen, Abteilung Neurologie, Robert-Koch-Str. 40, 37075 Göttingen, Germany
Prof. Dr. Cornelius Weiller, Prof. Dr. Achim Liepert	Universitätsklinikum Eppendorf, Klinik und Poliklinik für Neurologie, Martinistr. 52 / N24, 20246 Hamburg, Germany
Prof. Dr. Reinhard Dengler	Neurologische Klinik mit klinischer Neurophysiologie, Medizinische Hochschule Hannover, Carl-Neuberg-Str. 1, 30625 Hannover, Germany
PD Dr. Peter Urban, Dr. Andreas Fellgiebel	Johannes-Gutenberg Universität Mainz, Klinik und Poliklinik für Neurologie, Langenbeckstr. 1, 55101 Mainz, Germany
Prof. Dr. Wolfgang Oertel	Klinikum der Phillips-Universität Marburg, Abteilung Neurologie, Rudolf-Bultmann-Str. 8, 35039 Marburg, Germany
Prof. Dr. Gilberto Pizzolato, Dr Gianluigi Ricchierieri	Clinica Neurologica 1 – Departimento di Neuroscienze, Universitá di Padova, Via Giustiniani 5, 35128 Padova, Italy
Prof. Dr. Ubaldo Bonucelli	U.O. di Neurologia – Departimento di Neurologia, Universitá di Pisa, P.O. Santa Chiara – A.O. Pisana, Via Bonanno 54, 56126 Pisa, Italy
Prof. Dr. Dag Aarsland	Stavanger Universitetssjukehus, Dept: Psykiatrisk Klinikk, Alderspsykiatrisk Poliklinikk, PO Box 1163 Hillevåg, 4095 Stavanger, Norway
Dr. Maria M Pareira Costa	HPP Medicina Molecular, SA, Avenida da Boavista, 119, 4050-115 Porto, Portugal
Prof. Dr. Lars-Olof Wahlund	Karolinska Universitetssjukhuset, Huddinge, Hälsovägen, Flemingsberg, 14186 Stockholm, Sweden
Dr. Eduardo Tolosa Sarro	Hospital Clinic i Provincial, Unidad Memoria-Alzheimer, c/Villaroel, 170, 08036 Barcelona, Spain
Dr. Lorenzo Morlán Gracía	Hospital Universitario de Getafe, Servicio de Neurologia, Ctra. De Toledo km 12,5, 28950 Getafe, Madrid, Spain
Dr. J Andrés Burguera	Hospital Universitarion La Fe, Consultas de Neurologia. Planta Baja, Avda Campanar, 21, 46009 Valencia, Spain
Dr. Thomas Alan	Old Age Psychiatry Offices, Bensham General Hospital, Saltwell Road, Gateshead, NE8 4Yl, UK
Dr. Clive Holmes	Memory Study and Research Centre, Moorgreen Hospital, Botley, West End, Southampton, Hampshire, SO30 3JB, UK
Prof. Dr. Adrian Danek	Klinikum Großhadern der Ludwig-Maximilians-Universität, Klinik und Poliklinik für Neurologie, Marchioninistr. 15, 81377 München, Germany
Prof. Dr. Gerhard Ransmayr	Allgemeines Krankenhaus Linz, Abteilung Neurologie und Psychiatrie, Krankenhausstr. 9, 4021 Linz, Austria
Prof. Dr. Alessandro Padovani	Neurologia 2, Spedali Civili di Brescia, Piazzale Ospedale, 1, 25123 Brescia, Italy

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Prof. Dr. Jan Aasly	St Olavs Hospital, Dept: Nevologisk avdeling, Olav Kyrres gate 17, 7006 Trondheim, Norway
Prof. Dr. Ulla Passant	Universitetssjukhuset, Avd. For Geriatrisk Psykiatri, Klinikgatan 22, 22185 Lund, Sweden
Dr. Martin Bojar	Universitiy Hospital Motol, 2nd School of Medicine, Charles University Prague, V Uvalu 84, 150 06 Prague 5, Czech Republic
Dr. Naji Tabet	MRC Psych. Consultant and Senior Lecturer in Old Age Psychiatry, East Sussex County Healthcare NHS Trust, Beechwood Unit, Uckfield Community Hospital, Framfield Road, Uckfield, East Sussex, TN22 5AW, UK
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Prof. Dr. Alberto Albanese	Istituto Nazionale Neurologico “Besta”, Università Cattolica del Sacro Cuore, Via Caloria 11, 20133 Milano, Italy
Dr. Eulegio Gil Neciga	Hospital Virgen del Rocio, Neurologie, Avd de Manuel Siurot s/n, 41013 Sevilla, Spain
Ordination Dr. Michael Rainer	Lainzerstr. 20, 1130 Wien, Austria
Dr. Peter Bowie	Longley Centre, Norwood Grange Drive, Sheffield, S5 7JT, UK
Prof. Dr. Gordon Wilcock	BRACE Centre, Blackberry Hill Hospital, Fishponds, Bristol, BS16 2EW, UK
Dr. Rainhard Ehret	Schloßstr. 29, 12163 Berlin, Germany
Prof. Dr. Alexander Kurz	Psychiatrische Klinik der TU München, Moehlstr. 26, 81675 München, Germany
Prof. Dr. Jan Booij	Department of Nuclear Medicine, Academic Medical Centre, Meibergdreef 9, Postbus 22660, 1105 AZ Amsterdam Zuidoost, Netherlands
Prof. Dr. Jacques Darcourt	Laboratoire de Biophysique et Traitement de l’Image, Faculte de Medicine, Universitede Nice Sophia-Antipolis, 28 Avenue de Valombrose, 06107 Nice, Cedex 2, France
Prof. Dr. Klaus Tatsch	Ludwig-Maximilians Universität, Klinikum Großhadern, Abteilung für Nuklearmedizin, Marchioninistrasse 15, D-81377 München
Dr. Frode Willoch	Aker sykehus, Radiologisk avdeling, Trondheimsveien 235, 0514 Oslo, Norway
Dr. Zuzana Walker	University College London, Department of Mental Health Sciences, 48 Riding House Street, London, Win8AA, UK
Prof. Dr. Ian McKeith, Prof. Dr. John O'Brien	Newcastle General Hospital, Institute for Health and Aging, Newcastle uponTyne, NE4, 6BE, UK
CRL.Medinet (Europe)	Bergschot 71, P.O. Box 5510, 4801 DM Breda, The Netherlands
PDT304	
Dr. Donald Grosset, Dr. James Patterson,	Dept of Neurology, Southern General Hospital, 1345 Govan Road, Glasgow, G5I 4TF

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Angela O'Donnell, Mary Theresa Hansen, Bianca Holmes, David Brown, Tracey Jones, Katherine Grosset, Marlene Smeaton, Donald Hadley, Kate MacFarlane Bryce, Elaine Tyrell	
Prof. W Oertel, Anja Gerstner, Helmut Höffken, Prof. Joseph, Meike L Schipper, Doris Lang Pfeiffer, Aline Metz, Andreas Fischer, Martin Gotthardt, Sylvia Rura, Halina Pollum, Thomas Behr	Klinikum der Phillips - Universität Marburg, Med Zentrum for Nervenheilkunde, Klinik für Neurologie, Rudolf-Bultmann - Strasse 8, D 35039 Marburg, Germany
Dr. Hani BenAmer, Christopher Martin Boiven, Philip Anderson, Jillian Andrews, Susan Ackrill, Lindsey Halliburton, Jill Conley, Alan Deakin, Elizabeth McLelland, David Borell, Richard Michael Poyner	EEG Department, New Cross Hospital, Wednesfield Road, Wolverhampton, WV10 0QP, UK
Dr. Paul Kemp, Lucy Bolton, Helen Roberts, James Thom, Ian Gove, Livia Bolt, John S. Fleming, Sandra Johns, Maureen Zivanovic, Syed Zaman	Dept Nuclear Medicine, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK
Dr. David Burn, John Fenwick, Andrea Stutt, Una Brechany, Susan Faulkner, Sophie Molloy,	Newcastle General Hospital, Westgate Road, Newcastle upon Tyne, NE4 6BE, UK

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Dr. Jaime Kulisevsky, Berta Pascual, Ana M Catafau, Jolanda Aguilar Puente, Angel Hernandez Fructuoso, Antonia Campolongo, Montserrat Estorch	Sevicio de Neurologia, Hospital de la Santa Creu I Sant Pau, Paseo San Antonio Maria Claret 167, 08025 Barcelona, Spain
Dr. T van der Borght, Eric Mormont	Dept of Nuclear Medicine, University Hospital UCL, Mont-Godinne, 5530 Yvoir, Belgium
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Prof W Poewe, Prof Roy Moncayo, Georg Riccabona, Eveline M Donnemiller, Klaus Seppi, Boris Becket Aurel, Clemens Decristoforo, Michael Gabriel, Dirk Rudiger Hente	Leopold-Franzens-Universität, Innsbruck, Universitätsklinikum für Neurologie, Anichstr. 35, A-6020 Innsbruck, Austria
PDT408	
Prof. Eduardo Tolosa	Dept of Neurology, H. Clinic I Provincial, Barcelona, Spain
Dr. Ana Catafau	Dept of Nuclear Medicine, H. Sant Pau, Barcelona, Spain
Patrice Laloux, Thierry Vander Borght	University Hospital UCL, Mont-Godinne, B-5530 YVOIR, Belgium
Michel Van Zandijcke, Frank De Geeter	AZ St Jan, Ruddershove 10, B-8000, BRUGGE, Belgium
Alain Destee, Marc Steinling	Hôpital Roger Salengro-CHU de Lille, Rue du 8 Mai 1945, 59037 LILLE cedex, France
Lucette Lacomblez, Marie-Odile Habert	Hopital Pitie Salpetriere, 47-83 Boulevard de l'Hôpital, 75651 PARIS cedex 13, France

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Ulrich Bogdahn, Chr. Eilles	Universität Regensburg, Klinik und Poliklinik für Neurologie im Bezirksklinikum, Universistraβe 84, D-93053 REGENSBURG, Klinikum der Universitat Regensburg, Abt. f. Nuklearmedizin, Franz-Josf-Strauβ-Allee 11, D-93053 REGENSBURG, Germany
Anton Haas, Carl-Martin Kirsch	Universitätskliniken des Saarlandes, Kirrberger Straβe, D-66421, HOMBURG/SAAR, Germany
Angelo Antonini, Riccardo Benti	Centro Parkinson, C.T.O., Az. Osp. Istituti Clinici di Perfezionamento, Via Bignami 1, I-20126 MILAN, Ospedale Maggiore di Milano, I.R.C.C.S., Padiglione Granelli, Via F. Sforza 35, I-20122 MILAN, Italy
Sandro Sorbi, Alberto Pupi	Università di Firenze, Viale Morgagni 85, I-50134 FLORENCE, Italy
Luis Cunha, João Pedroso de Lima	Hospitais da Universidade de Coimbra, Av. Bissaya Barreto, P-3000-075 COIMBRA
Eduardo Tolosa, Francisco Lomeña	Hospital Clinic i Provincial, Villarroel, 170, E-08036 BARCELONA, Spain
Jaime Kulisevsky, Ana M Catafau	Hospital de la Santa Creu i Sant Pau, Paseo San Antonio María Claret, 167, E-08025 BARCELONA, Spain
Ray Chaudhuri, Muriel Buxton-Thomas	King's College Hospital, Denmark Hill, CAMBERWELL, SE5 9RS, UK
William RG Gibb, Paul M Kemp	Southampton General Hospital, Tremona Road, SOUTHAMPTON S016 6YD, UK
Susanne Asenbaum, Robert Dudczak	Allgemeines Krankenhaus der Stadt Wien, Währingergürtel 18-20, A-1090 VIENNA, Austria

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Table S2. Ethics Committees for the Four Studies in the Pooled Analysis

Study DP008-003

Committee Name	City	Country	Chairman
Medical Research Ethics Committee, The Phillips University Clinic	Marburg	Germany	Dr. P Heubel
The Faculty of Medicine Ethics Committee, Ludwig Maximilian University of Munich	Munich	Germany	Prof. Dr. med. Dent. W Gernet
Southern General Hospital Medical Ethics Committee	Glasgow	UK	Rev. D Keddie
Medical Ethics Committee, Academic Medical Center, Amsterdam University	Amsterdam	The Netherlands	Prof. L Arisz
Joint UCL/UCLH Committees on the Ethics of Human Research	London	UK	Prof. A McLean
Ethics Review Committee, University Hospital	Ghent	Belgium	Prof. Dr. M Bogaert

PDT301

Committee Name	City	Country	Chairman
Ethikkommission des Landes Oberösterreich	Linz	Austria	Univ. Prof. Prim Dr. Fisher
Ethik-Kommission der Medizinischen Fakultät der Universität Wien und des Allgemeinen Krnkenhauses der Stadt Wien AKH	Wien	Austria	Univ. Prof. Dr. E Singer
Comité consultative pour la protection des personnes dans la recherché biomédicale Bordeaux B	Bordeaux	France	Prof. MC Saux
Ethik-Kommission an der Medizinischen Fakultät der Universität Leipzig	Leipzig	Germany	Prof. Dr. med. R Preiß
Ethikkommission, Campus Charité Mitte	Berlin	Germany	Prof. Dr. med. R Uebelhack
Ethik-Kommission der Ruhr- Universität Bochum, Medizinischen Fakultät	Bochum	Germany	Prof. Dr. Zenz
Ethik-Kommission der Georg-August-Ruhr-Universität Göttingen	Göttingen	Germany	Prof. Dr. med. E Rüther
Ethik-Kommission der Ärztekammer Hamburg	Hamburg	Germany	Prof. Dr. med. Th. Weber
Medizinischen Hochschule Hannover, Ethikkommission	Hannover	Germany	Prof. Dr. HD Tröger
Landesärztekammer Rheinland-Pfalz, Ethikkommission	Mainz	Germany	Prof. Dr. Rittner

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Committee Name	City	Country	Chairman
Kommission für Ethik in der ärztlichen Forschung. Bereich Humanmedizin, Klinikum der Philipps- Universität Marburg	Marburg	Germany	Prof. Dr. Med. G Richter
Regione Veneto, Aziendo Ospedaliera di Padova, Comitato Etico per la Sperimentazione	Padova	Italy	Dr. R Pegoraro
Azienda Ospedaliera Pisana, Comitato etico per la studio del farmaco sull' uomo	Pisa	Italy	Prof. R Barsotti
Regional komité for medisinsk forskninsetikk, Vest-Norge (REK Vest), Universitetet i Bergen, det medisinske fakultet	Bergen	Norway	A Berstad
Comité Ético de Investigação Clinica	Porto	Portugal	
Karolinska Institutet, Forskningsettikkommitté Syd	Stockholm	Sweden	Prof. H Glaumann
Regionala etikprövningsnämnden i Stockholm	Stockholm	Sweden	Prof. LE Rutquist
Clinic Barcelona, Hospital Universitari, Comitè ètic investigaciò clinica	Barcelona	Spain	
Comité Etico de Investigación Clinica, Hospital Universitario de Getafe	Madrid	Spain	
Comité etico de investigación clinica Hospital "La Fe" Valencia	Valencia	Spain	
Northern and Yorkshire Multi-Centre Ethics Committee, Durham University	Durham	UK	J Kelly/S Brunton-Shiels
Gateshead Local research Ethics Committee	Sunderland	UK	Dr. DG Raw
Northumberland, Tyne and Wear NHS Strategic Health Authority Local Research Ethics Committees, Newcastle General Hospital	Newcastle upon Tyne	UK	Dr. J Lothian, PD Carr
Southampton & South West Hampshire Local Research Ethics Committee	Southampton	UK	C Wright
Ethikkommission der Medizinischen Fakultät der Ludwig-Maximilans-Universität, LMU, Klinikum Großhadern	München	Germany	Prof. Dr. G Paumgartner
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig
Aligemeines öffentliches Krankenhaus der Stadt Linz, Kommission zur Beurteilung klinischer Prüfungen von Arzneimitteln, Ethikkommission	Linz	Austria	Primar Dr. H Stekel
Ospedali Civili Brescia, Aziendo Ospedaliera, Comitato Etico	Brescia	Italy	Prof. F De Ferrari

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Committee Name	City	Country	Chairman
Fakultní nemocnice v Motole, Etickákomise	Prague	Czech Republic	MUDr. V Šmelhaus
Brighton and Sussex Local Research Ethics Committee	Brighton	UK	Dr. P Seddon
East Sussex Local Research Ethics Committee	Brighton	UK	Dr. J Rademaker
South Manchester Local Research Ethics Committee	Manchester	UK	Dr. W Pettit
Central Manchester Research Ethics Committee	Manchester	UK	Dr. D Mandal
NHS Tayside Board, Tayside Committee on Medical Research Ethics, Ninewells Hospital & Medical School	Dundee	UK	NF Brown
Fazio-Fondazione San Raffaele Del Monte Tabor Milano, Comitato Etico Dell'istituto Nazionale Neurologico Besta di Milano	Milano	Italy	Prof. E Müller
IRCCS – Fondazione San Raffaele Del Monte Tabor di Milano	Milano	Italy	Prof. G Zoppei
Comité ético de investigación clínica, Servicio Andaluz de Salud, Consejería de Salud, Hospitales Universitarios Virgen de Rocío de Sevilla	Sevilla	Spain	
Ethikkommission der stadt Wien	Wien	Austria	Dr. H Serban
North Sheffield Local Research Ethics Committee, Northern General Hospital	Sheffield	UK	Dr. G PM Clark
Glasgow West Local Research Ethics Committee	Glasgow	UK	Dr. J Hunter
NHS Greater Glasgow Primary Care Division Local Research Ethics Committee, Gartnavel Royal Hospital	Glasgow	UK	Dr. P Fleming
Frenchay Research Ethics Committee, North Bristol NHS Trust Headquarters	Bristol	UK	Drs. Kendall and M Shere
Ärztekammer Berlin, Ethik-Kommission	Berlin	Germany	C Biondo
Ethikkommission des Landes Bremen, Institut für Klinische Pharmaakologie, Klinikum Bremen-Mitte	Bremen	Germany	Dr. K Boomgaarden-Brandes
Ethikkommission der Fakultät für Medizin der Technischen Universität München	München	Germany	Prof. Dr. A Schömig

PDT304

Committee Name	City	Country	Chairman
Ethics Committee of the Southern General Hospital NHS Trust, Glasgow	Glasgow	UK	Rev. D Keddie

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Committee Name	City	Country	Chairman
Kommission für Ethik in der Ärztlichen Forschung, Klinikum der Philipps-Universität Marburg	Marburg	Germany	Prof. Dr. med. G Richter
New Cross Hospital Local Research Ethics Committee	Wolverhampton	UK	D.S.Little
Southampton and South West Hampshire Joint Local	Southampton	UK	Dr. A Kermode
Joint Ethics Committee Newcastle and North Tyneside Health Authority	Newcastle	UK	Prof. PA Heasman
Comite Etico de Investigacion Clinica Hospital Clinic I Provincial	Barcelona	Spain	Prof. J Rodes
Comite Etico de Investigacion Clinica del Hospital de la Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrenca
Comité d' éthique hospitalier, Cliniques Universitaires de Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Hospitais da Universidade de Coimbra	Coimbra	Portugal	Dr. JA Branquinho de Carvalho
Ethikkommission der Medizinischen Faultät der Universität Innsbruck	Innsbruck	Austria	Univ. Prof. Dr. P Lukas

PDT408

Committee Name	City	Country	Chairman
Hospital Ethical Committee, University Hospital UCL Mont-Godinne	Yvoir	Belgium	Dr. P Evrard
Commission for Ethics, AZ St.-Jan AV	Brugge	Belgium	Dr. J Van Droogenbroeck
Comite Consultatif de Protection des Personnes Dans La Recherche Biomedicale de Lille, Hôpital Huriez	Lille	France	Prof. PY Hatron
Ethik-Kommission der Ärztekammer Hamburg Kōrperschaft des ōffentlichen Rechts	Hamburg	Germany	Prof. Dr. Med. K Held
Ethikkomission des Klinikums der Universität Regensberg	Regensberg	Germany	Prof. Dr. R Andreesen
Vorsitzenden der Ethikkommission Bei der Ärztekammer des Saarlandes	Saarbrücken	Germany	Dr. S Ertz
Spett. Le Comitato Etico	Milano	Italy	Prof. A Randazzo
Comitato Etico Per La Sperimentazione Clinica Del Farmaci	Firenze	Italy	Prof. L Zilletti

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Committee Name	City	Country	Chairman
Ministério Da Saúde Hospitais Da Universidade De Coimbra	Coimbra	Portugal	Prof. Dr. JM Pedroso Lima
Comité Ético De Investigación Clínica Hospital Clínic I Provincial	Barcelona	Spain	Prof. MA Asenjo Sebastián
Comité Ético De Investigación Clínica Del Hospital De La Santa Creu I Sant Pau	Barcelona	Spain	FJ Carrencá
King's College Hospital	London	UK	Prof. ER Howard
Southampton and South West Hampshire Local Research Ethics Committees	Southampton	UK	Dr. A Kermode
Etik-Kommission Der Medizinischen Faultät der Universität Wien	Wien	Austria	Univ. Prof. Dr. E Singer

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Table S3. Demographic characteristics and clinical diagnosis (per Reference Clinical Diagnosis) by study – PP population (N = 622)

		Study				
		DP008-003 (N = 157)	**PDT304 (N = 100)**	**PDT301 (N = 288)**	**PDT408 (N=77)**	**Total (N = 622)**
Age (yr)	Mean (SD)	63.1 (8.51)	60.5 (10.97)	74.2 (7.02)	64.1 (12.05)	67.9 (10.61)
	Min, Max	40, 80	33, 79	54, 90	25, 84	25, 90
	Median	64.0	61.5	75.0	67.0	69.0
Gender	Male	99 (63%)	57 (57%)	160 (56%)	40 (52%)	356 (57%)
	Female	58 (37%)	43 (43%)	128 (44%)	37 (48%)	266 (43%)
Race	Caucasian	153 (97%)	100 (100%)	288 (100%)	76 (99%)	617 (99%)
	Black	3 (2%)	0 (0%)	0 (0%)	0 (0%)	3 (<1%)
	Asian	1 (1%)	0 (0%)	0 (0%)	1 (1%)	2 (<1%)
	Other	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PS (SDDD)		115 (73%)	69 (69%)	0 (0%)	47 (61%)	231 (37%)
Possible PS		115 (73%)	5 (5%)	0 (0%)	47 (61%)	167 (27%)
Probable PS		0 (0%)	64 (64%)	0 (0%)	0 (0%)	64 (10%)
DLB (SDDD)		0 (0%)	0 (0%)	110 (38%)	0 (0%)	110 (18%)
Possible DLB		0 (0%)	0 (0%)	25 (9%)	0 (0%)	25 (4%)
Probable DLB		0 (0%)	0 (0%)	85 (30%)	0 (0%)	85 (14%)
Non-PS/Non-DLB (no SDDD)		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)
ET		16 (10%)	14 (14%)	0 (0%)	23 (30%)	53 (9%)
AD		0 (0%)	0 (0%)	122 (42%)	0 (0%)	122 (20%)
Other		26 (17%)	17 (17%)	1 (<1%)	7 (9%)	51 (8%)
SDDD Present[a]		115 (73%)	69 (69%)	110 (38%)	47 (61%)	341 (55%)
SDDD Absent		42 (27%)	31 (31%)	123 (43%)	30 (39%)	226 (36%)

[a]Includes Possible and Probable PS and Possible and Probable DLB diagnoses.

AD = Alzheimer's disease; DLB = Dementia with Lewy bodies; ET = Essential tremor; N = number of subjects in the study; PP = Per protocol; PS = Parkinsonian syndrome; SD = standard deviation; SDDD = striatal dopaminergic deficit disorder.

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Table S4. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – ITD population (N = 726)[a]

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[b] – Baseline	91.1% (89.2 to 92.8)	92.3% (89.3 to 94.7)	78.5% (72.7 to 83.5)	90.1% (86.8 to 92.8)	88.7% (86.8 to 90.4)	91.2% (89.0 to 93.0)
Mean Results Across all Readers[c] – Month 12			78.5% (72.7 to 83.5)	92.8% (89.6 to 95.2)		
Mean Results Across all Readers[d] – Month 18	78.9% (72.8 to 84.2)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	76.6% (70.1 to 82.3)	96.7% (90.6 to 99.3)				

CI = Confidence interval; ITD = Intent to diagnose; NPA = Negative percent agreement; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a]PDT408 (N=78 for ITD) is included in the N. but not included in the mean calculations, as this study did not have blinded readers.

[b]Summary results calculated across all readers for studies DP008-003, PDT301, and PDT304 at baseline.

[c] Summary results calculated across all readers for study PDT301.

[d] Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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Table S5. Summary of sensitivity (PPA) and specificity (NPA) by expert clinical diagnosis – Means of individual blind reads – PP population (N = 622)[a]

Response	Expert Clinical Diagnosis					
	Parkinsonian Syndrome (PS; SDDD)		Dementia with Lewy Bodies (DLB; SDDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Mean Results Across all Readers[b] – Baseline	90.0% (87.6 to 92.0)	93.7% (90.4 to 96.2)	78.5% (72.7 to 83.5)	90.3% (87.0 to 93.0)	87.3% (85.1 to 89.3)	91.7% (89.5 to 93.7)
Mean Results Across all Readers[c] – Month 12			78.3% (72.5 to 83.4)	93.0% (89.8 to 95.4)		
Mean Results Across all Readers[d] – Month 18	78.3% (72.0 to 83.7)	95.7% (89.2 to 98.8)				
Mean Results Across all Readers[c] – Month 36	75.9% (69.3 to 81.7)	96.7% (90.6 to 99.3)				

CI = Confidence interval; NPA = Negative percent agreement; PP = Per Protocol; PPA = Positive percent agreement; SDDD = Striatal dopaminergic deficit disorder.

[a]PDT408 (N=77 for PP) is included in the N. but not included in the mean calculations, as this study did not have blinded readers.

[b]Summary results calculated across all readers for studies DP008-003, PDT301, and PDT304 at baseline.

[c]Summary results calculated across all readers for study PDT301.

[d]Summary results calculated across all readers for study PDT304.

Sensitivity/specificity for DLB is calculated based on Probable DLB vs. Non-DLB, and Total is calculated based on SDDD present vs. SDDD absent.

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STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-4
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	7
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	8-12, Table 1[a]
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	8-12[a]
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	8-13[a]
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	8-13[a]
Test methods	7	The reference standard and its rationale.	12-13, 24-25
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	12-13
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	12-13
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	8-13[a]
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	12-13
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	13-14
	13	Methods for calculating test reproducibility, if done.	14
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	7[a]
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	Tables 1, 2, & S3
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	Figure 1
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	13
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	Figure 2
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A[a]
	20	Any adverse events from performing the index tests or the reference standard.	N/A[b]
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	Figs 3 & 4, Tables 3, 4, S4, & S5
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A[a]
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	23, Tables 3, 4, S4, & S5

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	24	Estimates of test reproducibility, if done.	23
DISCUSSION	25	Discuss the clinical applicability of the study findings.	24-27

[a] Since this was a pooled analysis of 4 clinical trials and each of these individual studies have been previously published, some of these details are not included in this paper with the references provided. The individual primary publications of the 4 studies were referred to to obtain these details.
[b] Safety data were not a focus of the current report and will be published in a separate report.

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