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RESEARCH**

APPLICATION NUMBER:

022454Orig1s000

MEDICAL REVIEW(S)

January 3rd, 2010

Division of Medical Imaging and Hematology Products

Clinical Review of NDA re-submission following complete response letter

NDA: 22454 (Datscan)
PDUFA Date of re-submission: 1/14/2011
Product: Ioflupane I 123
Sponsor: GE Healthcare
Document Reviewer: Phillip Davis, MD

I. Executive Summary

This 11/16/2010 submission is a resubmission of NDA 22454, containing the sponsor's responses to the complete response letter issued by the Agency 12/23/2009. The sponsor has responded to the comments and requests in the complete response letter, and the resubmission contains the following: 1) an amended label with the requested controlled substance text, 2) a safety update, 3) a complete protocol for one of two separate PMC studies (to evaluate DaTscan image results agreement among non-Caucasian and Caucasian subjects), 4) a request for a proprietary name request, and 5) a request to be released from the PMC to study the effects of dopaminergic drugs on DaTscan results. In the clinical reviewer's opinion, this NDA re-submission is approvable.

II. Complete Response Letter Issues

[The issues outlined in the 12/23/2009 Complete Response letter are provided verbatim (with bold headings), followed by the clinical reviewer's comments on the responses to these issues provided in the sponsor's 11/16/2010 re-submission.]

CLINICAL

The proposed package insert (received on December 17, 2009) did not include the text necessary to support the approval of a controlled substance.

- a. Supply a revised label that incorporates this text.
- b. Alternatively, verify that this text does not apply to DaTscan, based upon findings from the Drug Enforcement Administration.

Reviewer's Comments:

The sponsor has added the following new information to the package insert:

DaTscan (Ioflupane I 123 Injection) for Intravenous Use, **CII**
Initial U.S. Approval: 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance

FULL PRESCRIBING INFORMATION

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance

As seem below, the sponsor has added the CII symbol to the vial and shield (container) labeling.

(b) (4)

Assessment

The revised labeling is acceptable (in format and content) from the clinical perspective. Please note a CMC review of the container labeling is pending.

LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Reviewer's Comments:

Please see above reviewer's comments under clinical section regarding new information contained in the submitted label.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

Reviewer's Comments:

Review of the sponsor's provided safety update reveals no new safety signals. Thus, the safety update requirement has been fulfilled.

POSTMARKETING ISSUES

Several issues pertinent to clarifying the safety or efficacy of this product require additional information that may be obtained from postmarketing studies or clinical trials. We understand that you are refining your clinical development plans, in response to our letter of September 8, 2009. We reiterate our postmarketing requests from that letter. Specifically, we request that you propose studies and/or clinical trials to address the following issues:

- 1) To conduct a clinical trial that assesses the agreement between DaTscan imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients. The trial will be designated and conducted in a manner that allows a comparison of the results between the non-Caucasian and Caucasian patients.

- 2) To conduct a clinical trial that assesses the impact of dopaminergic drugs upon DaTscan results. In addition to any other drugs, levodopa and carbidopa effects should be studied in this trial. Describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. Your response should include:
 - A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.
 - The proposed schedule for conducting the study/clinical trial, including all major milestones for the study/clinical trial, e.g., submission to the FDA of the finalized protocol, initiation of an animal or clinical study, completion of patient accrual, completion of the study/clinical trial, and submission of the final report, with accompanying SAS datasets and applicable revised labeling.

Reviewer's Comments:

1. The resubmission contains a complete clinical protocol (GE-001-011) to address the Post-Approval Commitment for a study of DaTscan imaging in non-Caucasians. This protocol was submitted under IND 101,016 and was acceptable in the clinical reviewer's opinion. A complete clinical protocol review will be filed separately in DARRTS.

2. The resubmission contains a request to be released from the Post-Approval Commitment to study the effects of dopaminergic drugs on DaTscan images. The justification of this request was submitted under IND 101,016. The clinical team deferred judgment on this request to the clinical pharmacology team. The pharmacology team has expressed the opinion that the sponsor's release request is acceptable.

III. Assessment and Plan

The sponsor has addressed the issues in the 12/23/2009 complete response letter. The sponsor's responses are acceptable to the clinical reviewer. The clinical reviewer recommends approval of the application provided:

The container labeling is acceptable to the CMC team.

* Of note, there is a pending proprietary name review by DMEPA.

[The 5/29/2009 and 12/14/2009 reviews by DMEPA and the 5/7/2009 review by DDMAC found the name to be acceptable. More than 3 months have passes since the last review.]

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/s/

PHILLIP B DAVIS
01/03/2011

LIBERO L MARZELLA
01/03/2011

Summary Review for Regulatory Action

Date	December 22, 2009
From	Dwaine Rieves, MD
Subject	Division Director Summary Review Acting Office Director/over Holidays
NDA/BLA #	22-454
Supplement #	Initial response to CR letter of September 8, 2009
Applicant Name	GE Healthcare
Date of Submission	October 26, 2009
PDUFA Goal Date	December 27, 2009
Proprietary Name / Established (USAN) Name	DaTscan Ioflupane I 123
Dosage Forms / Strength	Single-use vials containing 5 mCi I 123 Ioflupane in 2.5 mL solution (acetate buffer); 0.1 mcg ioflupane per mL
Proposed Indication(s)	DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.
Action/Recommended Action for NME:	<i>Complete Response</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Phillip Davis, MD
CDTL Review	Libero Marzella, MD, PhD
OSE/DMEPA	Denise Baugh, PharmD
Controlled Substance Staff	Char Reissing, PhD/Corinne Moody, analyst

DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This submission was a response to a Complete Response/Review (CR) letter issued on September 9, 2009. The CR letter deficiencies pertained to two aspects:

- a need for a revised package insert to address textual deficiencies
- a need for two postmarketing study commitments.

The sponsor responded in a manner that addressed all the deficiencies. However, during the review cycle, the team requested a review by the FDA Controlled Substances Staff (CSS) due to the nature of the drug (a derivative of cocaine). FDA CSS determined that the drug could only be approved with labeling that identified it as a schedule II narcotic/

(b) (5)
(b) (5)
approval at the present time necessitates identification of DaTscan as a schedule II narcotic within the package insert.

GE Healthcare does not concur with the FDA-requested labeling text that cited the schedule II narcotic status. Hence, the FDA will issue a CR letter, again requesting the schedule II narcotic text within the package insert. All other aspects of the September 9, 2009 CR letter have been addressed.

(b) (5)

2. Background

The active drug substance in DaTSCAN is ^{123}I -ioflupane, a molecule with affinity for the DaT. DaT has been shown to be prevalent within the striatum, a portion of the brain that consists of two major parts within each cerebral hemisphere, the caudate and putamen. The presence of DaT on the surface of dopaminergic neurons assists in the recycling (uptake) of dopamine back into the neurons. Exploiting the DaT affinity of ^{123}I -ioflupane, the applicant proposed that injection of ^{123}I -ioflupane (DaTSCAN) into humans allowed visualization of the striatum on SPECT imaging and implicitly, the detection of abnormal distribution of DaT and/or dopaminergic neurons throughout the striatum. The imaging results may assist in the evaluation of patients with tremor.

Two clinical studies evaluated the use of DaTscan among patients with tremor. These studies described the diagnostic performance of the test. DaTscan has a favorable risk to benefit profile (11 to 2) decision at an August 11, 2009 FDA advisory committee.

3. CMC/Device

All CMC issues were resolved during the initial review cycle. This CR response contained no CMC information.

4. Nonclinical Pharmacology/Toxicology

All nonclinical pharmacology/toxicology issues were resolved during the initial review cycle. This CR response contained no new information.

5. Clinical Pharmacology/Biopharmaceutics

Clinical pharmacology issues were resolved during the initial review cycle. This CR response contained no new information with the exception of a proposal for the study of 30 patients to assess the impact of certain dopaminergic-type drugs upon DaTscan imaging results.

6. Clinical Microbiology

No new information was supplied/no outstanding issues.

7. Clinical/Statistical-Efficacy

I concur with Dr. Davis' observation that the sponsor resolved all the package insert labeling issues except for those pertaining to the schedule II status of the drug.

8. Safety

No new safety concerns were identified in the supplied data.

9. Advisory Committee Meeting

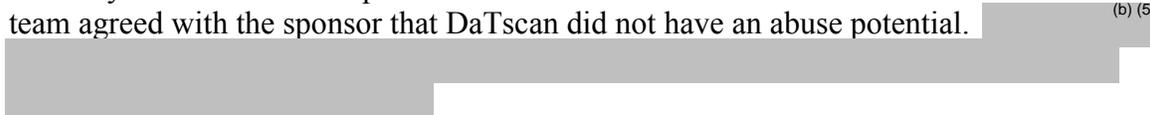
As noted above/DaTscan was reviewed at an August, 2009 advisory committee.

10. Pediatrics

Clinically uncertain PS was regarded as not applicable to the pediatric patient population and pediatric studies were waived.

11. Other Relevant Regulatory Issues

The only unresolved issues pertain to the controlled substance situation. The division review team agreed with the sponsor that DaTscan did not have an abuse potential. (b) (5)



12. Labeling

As noted above, the controlled substance issue remains to be resolved.

13. Decision/Action/Risk Benefit Assessment

We plan to recommend issuance of a CR letter.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22454

ORIG-1

GE HEALTHCARE
INC

DA TSCAN

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/s/

RAFEL D RIEVES
12/22/2009

Cross-Discipline Team Leader (CDTL) Review

Date	December 16 , 2009
NDA #	22454
Supplement #	S-001
Applicant Name	GE HealthCare
Date of Submission	October 26, 2009
PDUFA Goal Date	December 24, 2009
Proprietary Name	DaTscan
Established (USAN) Name	Ioflupane I-123
Dosage Form / Strength	Injection/ 2mCi/ml
Proposed Indication	SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes
Reviewer	Libero Marzella M.D., Ph.D.
Recommended Action	Complete Response

1. Summary

The Applicant submitted this supplement to respond to the CR letter issued by FDA on September 8, 2009.

The review team recommends a complete response action because of outstanding labeling and postmarketing study issues.

2. CMC

Not applicable

3. Nonclinical Pharmacology/Toxicology

Not applicable

4. Clinical Pharmacology/Biopharmaceutics

FDA requested a commitment to conduct a clinical trial that assesses the impact of dopaminergic drugs upon DaTscan image results. In addition to any other drugs, levodopa and carbidopa effects would be studied in this trial.

At the time this review was written no agreement on the design of a drug interaction study had been reached with the Applicant.

5. Clinical Microbiology

Not applicable

6. Clinical/Statistical-Efficacy

The CDTL agrees with the FDA clinical reviewer's recommendation for a complete response action.

Dr. Davis conducted a complete review that addressed all the relevant issues and identified the following major outstanding deficiencies

- 1) The request by CSS that the package insert reflect the current status of the drug as a narcotic substance under the Controlled Substances Act has not been addressed. At the time of the completion of the clinical review the Applicant had not agreed to revise the package insert with this change.
- 2) The package insert needs to include the statement that the effectiveness of Datscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established. The reviewers recommend that this statement be added to the Clinical Studies section of the label.

A number of claims have appeared in the literature about the utility of investigational radiopharmaceuticals (e.g. F18-DOPA) for assessment of pre-synaptic dopaminergic function. The claims include confirmation of disease diagnosis and evaluation of disease progression and do not appear to be based on substantial evidence. The labeling statement proposed by Dr. Davis is meant to prevent potential ambiguity about the clinical utility of DaTscan. The reviewers believe that the statement is clear and is not unduly prominent.

- 3) In the clinical review Dr. Davis notes that no agreement has been reached with the Applicant on the design of the postmarketing clinical study of DaTscan in non-Caucasian patients. FDA had requested that the Applicant commit to conduct a clinical trial that assesses the agreement between DaTscan imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients. This trial would be designed and conducted in a manner that allows a comparison of the results between the non-Caucasian and Caucasian patients.

In informal discussions with the Division the Applicant proposed a revised study design to address the anticipated difficulty in recruitment of such patients. At the time of this review the Applicant had not provided a revised study synopsis.

Finally, Dr. Davis also recommended other relatively minor label revisions in the Clinical Study section that the CTDL agrees ought to be made.

The submission did not require a statistical review.

6. Clinical Safety

As noted in the clinical review no new safety issues have emerged based on clinical trial data and spontaneous adverse reaction reports from non-US sources.

7. Consultations

Controlled Substances Staff (CSS)

The FDA CSS analyst Ms. Moody determined that the active pharmaceutical ingredient (API) of the product [REDACTED] (b) (4) is a derivative of cocaine. CSS determined that if the API is derived from cocaine [REDACTED] (b) (4), it is by definition a Schedule II narcotic substance in the Controlled Substances Act (CSA).

CSS noted DMIHP's opinion that DaTscan has no abuse potential and that it should be considered for exemption from CSA regulations. [REDACTED] (b) (5)

The FDA CSS pharmacologist Dr. Reissig determined that the drug's status as a controlled substance must be clearly marked on the outside of the product packaging and in the highlights of the prescribing information by including the "CII" symbol after the commercial name. In addition Section 9, Drug Abuse And Dependence needs to contain the following language: "loflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act."

Division of Medication Error Prevention and Analysis (DMEPA)

The FDA DMEPA Safety Evaluator Dr. Baugh, conducted a review of the revised proprietary name with special emphasis on risk assessment. Dr Baugh determined that the proposed name, DaTscan, is not vulnerable to name confusion that could lead to medication errors nor is the name considered promotional. Thus DMEPA has no objection to the proprietary name for this product at this time.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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/s/

LIBERO L MARZELLA
12/17/2009

December 14th, 2009

Division of Medical Imaging and Hematology Products

Clinical Review of NDA resubmission following complete response letter

NDA: 22454 (Datscan)
Approval Date: Under review
PDUFA Date of submission: 12/24/2009
Product: Ioflupane I 123
Sponsor: GE Healthcare
Document Reviewer: Phillip Davis, MD

I. Summary

This submission contains the 10/26/2009 resubmission of NDA 22454, with the sponsor's responses to the complete response letter issued by the Agency 9/8/2009. The sponsor has responded to all questions/comments/requests in the complete response letter, and has provided an amended label, along with protocol synopses of phase 4 PMC studies and an image interpretation workbook. A detailed review of the complete response letter issues with sponsor's responses and MO comments to these responses is in section III below.

II. Assessment and Plan

The sponsor has adequately addressed all issues in the complete response letter. The sponsor's responses are acceptable and well justified. This reviewer recommends approval of the application if agreement is reached to add the following statements to the package insert:

1. Ioflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act.
2. The effectiveness of Datscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established.

* Of note, separate reviews will be filed in DARRTS for the phase 4 PMC studies and the image interpretation workbook.

III. Controlled Substance Issues

DMIHP consulted the FDA controlled substance staff (CSS) to make a determination as to Datscan's abuse potential and whether it should be exempted from control under the Controlled Substances Act (CSA). The division agreed with the sponsor that Datscan has no abuse potential and that it should be considered for exemption from CSA regulations. Following review of the Datscan consult, CSS reached the conclusion that since the active ingredient, and all chemical intermediaries, of Datscan are derivatives of cocaine, then Datscan is by definition a Schedule II narcotic substance under the CSA. The CSS recommends the sponsor contact the Drug Enforcement Administration (DEA) to discuss the CSA control status of Datscan and whether the DEA will consider Datscan for exemption from CSA controls. Thus, if agreement is reached for the package insert

issues discussed in section II, then Datscan is recommended for approval as a controlled substance. If the sponsor wishes to pursue exemption from CSA controls, the sponsor will need to discuss this issue with the DEA.

IV. Complete Response Letter Issues

[The issues outlined in the Complete Response letter are provided verbatim, in ***bold and italics***, followed by the sponsor's response and clinical reviewer's comments.]

CLINICAL

1. The proposed package insert (received on September 3, 2009) contained several items that require clarification, justification or redevelopment. Supply information and a revised package insert that addresses the following items:

a. The proposed indication does not clearly define "Parkinsonian syndromes (PS)" and appears promotional in tone. Redevelop the proposed indication statement to clearly define PS and to delete the phrase that notes, [REDACTED] (b) (4) [REDACTED]. We supplied a draft "indication" proposal to you on September 1, 2009, that contained the items we regarded as important for your labeling. Several aspects of our proposal were not incorporated into your subsequent revision and your deletions were inadequately justified. Redevelop the "indication" statement within your proposed package insert to address the items cited in our September 1, 2009, proposal.

Sponsor Response: We have redeveloped the Indications and Usage statement that follows the September 1st FDA proposal, with the following distinctions:

We are suggesting the phrase "suspected Parkinsonian syndromes (PS)" instead of [REDACTED] (b) (4) as we consider the terms to be essentially equivalent, but with "suspected" being a more commonly used term when considering diagnosis. Therefore, we believe it will resonate more with physicians.

We are proposing the deletion of the [REDACTED] (b) (4) statements that appear to be unwarranted and unsubstantiated. Our justification for deletion of these statements is based upon the following four points:

1. The Physician Labeling Rule (PLR) does not require that the Indications and Usage section of the labeling state the uses for which a drug is NOT approved, but rather must state what the drug "is indicated for". Supporting this argument, 71 Fed. Reg. 3922, 3944 (January 24, 2006)(preamble to final rule) states "FDA believes practitioners... understand that the uses described in this section are those for which FDA has found to be safe and effective."
2. The PLR does require that the Indications and Usage section contain major limitations of use [21 CFR 201.57I(2)(i)(A)-(F)], which include:
 - i. Drug used "only in conjunction with a primary mode of

therapy”

- ii. Drug that is safe and effective “only in selected subgroups”
- iii. “Tests are necessary” for selection of patients who need the drug
- iv. “Information on limitations of use or uncertainty about anticipated clinical benefits” that is relevant to intervals between doses, duration of treatment or modification of dosage
- v. Drugs used only in specific situations because of “safety considerations”
- vi. “Specific conditions” that should be met before drug can be used long term

The FDA proposed language for DaTscan, (b) (4)

does not appear to be covered by any of these listed major limitations of use.

3. The Indications and Usage section must state if there is a “lack of evidence” supporting safety or effectiveness of common off-label use.

The PLR states:

“If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.”

(b) (4)

4. Including in the Indications and Usage section the uses for which a drug is not indicated undermines drug labeling. As the FDA noted in the preamble to the PLR, healthcare practitioners understand that the uses listed in the drug label are approved by the FDA, and that uses not listed are not FDA-approved. If the FDA requires listing uses that are approved and are not approved, practitioners may become confused about uses that are not listed. Before the FDA can list on labels uses that are not approved, they must first conduct cognitive research to determine the effects of such a change according to 71 Fed. Reg. 3922, 3930-21 (January 24, 2006) (preamble to final rule) (citing cognitive research and Agency’s employment of “cognitive principles”). In the context of DaTscan, we believe that FDA should not begin requiring manufacturers

to list in the Indications and Usage section of labels uses that are *not* approved without first conducting cognitive research to determine the effect of such a change, i.e., whether such a practice would (1) confuse practitioners, (2) deter lawful off-label prescribing to the detriment of patients, (3) promote off-label prescribing to the detriment of patients, or (4) have some other unintended effect.

Reviewer's comments

The sponsor's responses are acceptable and the redeveloped "indication and usage" statement for the label is acceptable.

b. With respect to the "Thyroid Blockade" portion of your September 3, 2009, proposed package insert, you have stated that

stated that prescribers should,

Summarize the "thyroid blocking" procedures used in your clinical trials and those currently recommended within your marketing experience outside the United States.

Sponsor Response: Our current position is to recommend thyroid blockade before administration of DaTscan. Different centers have different protocols for thyroid blockade and this is reflected in the protocols or reports of the DaTscan clinical trials submitted in the NDA:

CY95 FP1: Oral potassium iodide solution (total 230 mg of a 10% solution) the day before and during the day of the study.

CY96 FP2: The thyroid blocking protocol required the self administration of 99mg of potassium iodide (equivalent to 30 drops of a 10% iodide solution) taken orally 1 day prior to the next visit, visit 2, and a further 66 mg of potassium iodide (equivalent to 20 drops of a 10% iodide solution) on the morning of visit 2 prior to presentation at the study site.

PDT02005: One to two hours prior to injection each subject was placed on a thyroid blocking protocol. Prior to administration of DaTscan each subject underwent a thyroid blocking procedure involving the administration of potassium iodide at a volume of 2.5 ml.

DP008-003: No mention is made of thyroid blockade in the Protocol. From the data listings it is apparent that not all subjects were blocked.

PDT304: Prior to the administration of DaTscan each subject will receive a thyroid blocking preparation, in accordance with each study centre's thyroid blocking protocol.

PDT03007: Each subject will be administered an iodine preparation, in accordance with each study site's thyroid blocking protocol, to establish a complete block prior to the administration of DaTscan.

PDT301: Subjects must undergo appropriate thyroid blocking treatment prior to injection to minimize thyroid uptake of radioactive iodine, for example by oral administration of approximately 120 mg potassium iodide 1 to 4 hours prior to

injection and again 12 to 24 hours post-injection of DaTscan.

PDT408: Prior to the administration of DaTscan each subject will be administered an iodine preparation, in accordance with each study centre's thyroid blocking protocol, to establish a complete thyroid block, i.e. oral administration of approximately 120 mg potassium iodine 1-4 hours prior to injection and again 12-24 hours post-injection of DaTscan.

GE-001-WALKER: Potassium iodate was administered prior to DaTscan injection to block any potential uptake of radioactive iodine by the thyroid gland.

The current situation in Europe is that most centers perform thyroid blocking before and after administration of DaTscan, because it is stated in the Summary of Product Characteristics (SPC), although many consider it is not necessary. The current SPC throughout Europe contains the following concerning thyroid blockade: "Patients must undergo appropriate thyroid blocking treatment prior to injection to minimise thyroid uptake of radioactive iodine, for example by oral administration of approximately 120 mg potassium iodide 1-4 hours prior to injection and again 12-24 hours post-injection of DaTSCAN."

(b) (4)

We therefore propose the following statement in connection with the use of the product in the US, which is also consistent with the prescribing information for AdreView™ (Iobenguane I 123 Injection) (NDA 22-290):

2.2 Thyroid Blockade Before DaTscan Injection

Before administration of DaTscan, administer Potassium Iodide Oral Solution or Lugol's Solution (equivalent to 100 mg iodide) or potassium perchlorate (400 mg) to block uptake of iodine 123 by the patient's thyroid. Administer the blocking agent at least one hour before the dose of DaTscan [*see Warnings and Precautions (5.2)*].

Brief Justification: Blockade of the thyroid before administration of DaTscan is desirable, affording a significant reduction in the radiation absorbed dose to the thyroid. DaTscan contains very low levels of radionuclidic impurities, [¹²³I]ioflupane is not de-iodinated *in vivo*, iodine-123 has a physical half-life of 13 hours and blood clearance is rapid. The blocking effects of stable iodide last for many hours, and so there is no need for the second administration of a blocking agent 12 to 24 hours after DaTscan administration.

Rationale: Blockade of the thyroid gland is a measure routinely employed in departments of nuclear medicine to reduce undesirable or unintended thyroid uptake of radioactive iodide and hence to reduce the radiation dose to the thyroid. It is performed particularly in circumstances where the adventitious absorbed dose, and hence the risk, to the thyroid might be high. For a 185 MBq administration of the Drug Product, DaTscan, the maximum absorbed radiation dose to the unblocked thyroid gland is estimated to be 39.9 mGy. This includes contributions from the

biodistribution and thyroid uptake of the maximum permissible content of radiochemical (6% free iodide) and radionuclide (0.1% ^{125}I) impurities.

For more typical levels of radiochemical and radionuclide impurities, the dose to the unblocked thyroid is calculated to be 19.6 mGy. Over 90% of this dose is due to the presence of free iodide in the injection. The radiation dose to the thyroid can be reduced to 1.7 mGy by pre-administration thyroid blockade using one of the protocols recommended in the proposed labeling.

In circumstances where exposure to radioactive iodine could be prolonged, continued prophylaxis is recommended. In the case of DaTscan this is not necessary. The only source of exposure to free iodide is that which is present in the injection. Ioflupane is not de-iodinated *in vivo*. For this to occur it is a prerequisite that an oxidizable group is in either the *ortho*- or *para*- position with respect to the iodine group. In the ioflupane molecule, the tropane ring, *para*- to the iodine atom, is unable to undergo the oxidation reaction necessary for *in vivo* oxidative cleavage of the carbon-iodine bond so no *in vivo* de-iodination should be observed. This is confirmed by the biological data. For example, Baldwin et al. (1995) studied [^{123}I]ioflupane in adult female baboons and noted that there was no indication of release of iodide ion, as radioactivity in the thyroid gland did not show significant uptake over background, even though the thyroid was not blocked with stable iodine. In the human studies performed by Tanaka et al. (1999), analysis of plasma and urine samples out to 24 hours post injection of [^{123}I]ioflupane indicated to the authors that “*in vivo* de-iodination was minimal”. In the MIRD Dose Estimate Report No. 5 on radioactive iodides (Berman et al. 1991) biodistribution data for intravenously administered iodide indicate that by 6 hours post-injection, only 9% remains in the blood and by 24 hours this had fallen to 1.6% with over 75% of the administered activity being excreted. In the extreme case of a 6% iodide radiochemical impurity at the time of injection, whole body retention of [^{123}I]iodide at 24 hours post-injection of DaTscan would therefore be 25% of 6% of 185 MBq, which would also have undergone approximately 2 physical half-lives. The amount of residual iodide available for uptake into the thyroid after DaTscan imaging has been completed is therefore minute, amounting to a total of less than 1 MBq at 24 hours. If all of this were available for uptake by the thyroid the resulting radiation absorbed dose to the thyroid would be 3.2 mGy.

It should also be noted that the duration of protection afforded by a 100 mg blocking dose of stable iodide administered before exposure to radioactive iodide lasts for a number of days (Verger et al. 2001). The thyroid uptake of iodide is reduced by 78% and 25% at 48 and 72 hours respectively following stable iodide blockade. The pre-DaTscan blocking dose would thus continue to be effective in blocking thyroid uptake of iodide until only negligible amounts remained following biological clearance and physical decay. For these reasons a second administration of a thyroid blocking agent is not needed.

Finally it is noted that for the recently approved product AdreView (Iobenguane I 123 Injection) there is a recommendation for thyroid blockade before administration, but not afterwards. This product is administered at twice the radioactivity dose of DaTscan (370 MBq rather than 185 MBq) and has similar whole body clearance of ¹²³I radioactivity with minimal *in vivo* de-iodination. DaTscan is indicated for use in adults only. AdreView is indicated for use not only in adults but also in pediatric subjects in whom it would be more important to minimize the effects of thyroid irradiation. A requirement for a post-injection administration of a thyroid blocking agent is thus not supported by the biological and physical data and would also be inconsistent with the labeling of other iodine-123 labeled radiopharmaceuticals approved for use in the US.

Reviewer's comments

This clinical reviewer believes the sponsor has provided adequate justification to recommend blocking the thyroid gland only before Datscan administration. No further information or justification is required, the reviewer agrees with the sponsor's proposal.

c. The "Image Interpretation" section of your proposed package insert notes that,

Justify this contention, based upon your clinical trial experience and describe your plans for the development of any "instructional manuals" or other documents intended to assist in "Image Interpretation." Supply a copy of these documents.

Sponsor Response:

we apologize for our rephrasing being misleading. We have removed our suggestion from this section. Per your request, we have enclosed a draft copy of our Image Interpretation Workbook that will be provided to US customers.

Reviewer's comments

The sponsor's response is acceptable. In general, the content in the image interpretation workbook is acceptable. Please see the separate review document (DARRTS) for the image interpretation workbook for a detailed review of this information.

d. Justify your decision to delete the following statement from your package insert, "Failure to block thyroid uptake of iodine 123 may result in an increased long term risk for thyroid neoplasia." Consider other marketed radioactive iodine-containing products.

Sponsor Response: Considering other marketed radioactive iodine-containing products, we have removed our proposal from this section.

Reviewer's comments

The sponsor's response is acceptable.

e. Your September 3, 2009, submission contained new data and information that was supplied following completion of our review. This information (pertaining to the use of DaTSCAN among nursing mothers) will be reviewed following your response to this letter. To facilitate this review, we encourage you to highlight the basis for your "Nursing Mothers" proposal within your response.

Sponsor Response: Considering other marketed radioactive iodine-containing products, we have removed our proposal from this section.

Reviewer's comments

The sponsor's response is acceptable.

f. Justify your contention that,

(b) (4)

Sponsor Response:

(b) (4)

we have removed our proposal to delete this text in the absence of clinical data to establish a lack of an effect.

Reviewer's comments

The sponsor's response is acceptable.

g. Regarding the "Clinical Studies" section of the package insert: Revise this section within your subsequent submission to address the items you deleted from our September 1, 2009 package insert proposal. In particular, we object to the pooling of data across readers, the use of the terms (b) (4), and the inclusion of healthy volunteers in the Study 2 summaries. Additionally, justify the deletion of the statement that noted, "Study 1 readers had no other role in patient assessment; Study 2 readers included the investigators." We disagree with your overall approach that appears to support the use of DaTSCAN as a test with greater clinical impact than is consistent with the available clinical trial data. We described the many limitations with your clinical trials at the August 11, 2009 Advisory Committee presentation and we regard these limitations as also limiting the ability to describe performance

characteristics within your package insert.

Sponsor Response: We acknowledge your objections to our proposals and have removed them from this section. You will find, however, some minor textual modifications for your consideration.

Reviewer's comments

The sponsor's response is acceptable. We will make additional minor edits to the clinical studies section of package insert, such as removing the (b) (4)

The sponsor will recalculate the results (b) (4)
We will also add the statement "The effectiveness of Datscan as a screening or confirmatory test and for monitoring disease progression or response to therapy has not been established".

2. Contingent upon your response to the labeling items listed above, we may request additional information or further label revisions.

Sponsor Response: GE Healthcare will be happy to discuss any comments the FDA review team may have in relation to our draft labeling text.

Reviewer's comments

The sponsor's response is acceptable, nothing to add.

LABELING

We reserve further comment on the proposed labeling until the application is otherwise adequate. If you revise labeling, your response must include updated content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>.

Sponsor Response: Enclosed please find updated content of labeling in SPL format.

Reviewer's comments

The sponsor's response is acceptable. We will make additional minor edits to the resubmitted label.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

Sponsor Response: There are no significant changes or findings in the safety profile. There are no new nonclinical safety data on either the drug substance (ioflupane/FP-CIT) or the drug product (DaTscan). With regard to clinical, study PDT409 is ongoing but safety data are not yet available from this study. Study PDT409 has enrolled 224 subjects as of the cutoff date of September 22, 2009 and no serious adverse events (SAEs) have been reported.

Furthermore, there has been no spontaneous report of an adverse reaction following DaTscan administration in Europe within this reporting interval of June 18, 2009 (day after the last reporting interval summarized in the 4-month safety update report submitted on July 7, 2009/Sequence 0007) to September 22, 2009.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- **Present new safety data from the studies/clinical trials for the proposed indication using the same format as the original NDA submission.**
- **Present tabulations of the new safety data combined with the original NDA data.**
- **Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.**
- **For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.**

Response: There has been no newly completed clinical study from which to report safety data.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

Sponsor Response: There has been no newly completed clinical study from which to report safety data.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

Sponsor Response: There has been no newly completed clinical study from which to report safety data.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.

Sponsor Response: There has been no newly completed clinical study from which to report safety data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of

subjects, person time).

Sponsor Response: As reported in the NDA, Study PDT409 ended enrollment in Europe with 201 subjects as of October 29, 2008. An additional 23 subjects have enrolled in the US as of the cutoff date of September 22, 2009.

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

Sponsor Response: During this reporting interval of June 18, 2009 to September 22, 2009, there has been no spontaneous report of a patient experiencing an adverse reaction. Approximately (b) (4) vials of DaTscan have been sold in a total of 32 countries within this reporting interval of June 18, 2009 to September 22, 2009 and it can be estimated that the same number of doses were administered to patients.

8. Provide English translations of current approved foreign labeling not previously submitted.

Sponsor Response: No new foreign registrations have been obtained since the initial filing of the NDA.

Reviewer's comments

All of the sponsor's responses for the above safety update issues are acceptable, there are no additional safety issues to address at this point.

POSTMARKETING ISSUES

Several issues pertinent to clarifying the safety or efficacy of this product require additional information that may be obtained from post-marketing studies or clinical trials. We request that you propose studies and/or clinical trials to address the following issues:

1) To conduct a clinical trial that assesses the agreement between DaTSCAN imaging results and diagnostic outcomes among non-Caucasian and Caucasian patients. This trial will be designed and conducted in a manner that allows a comparison of the results between the non-Caucasian and Caucasian patients.

Sponsor Response: Enclosed please find a clinical protocol synopsis of our proposed non-Caucasian study [section 2.7.6, page 66] to address the question of whether or not race affects agreement between DaTscan imaging results and diagnostic outcomes.

2) To conduct a clinical trial that assesses the impact of dopaminergic drugs upon DaTSCAN image results. In addition to any other drugs, levodopa and carbidopa effects will be studied in this trial.

Sponsor Response: Enclosed please find a clinical protocol synopsis of our proposed drug interaction study [section 2.7.6, page 60] to address the question of whether or not dopaminergic drugs have an impact on DaTscan imaging results.

Describe your plans to address the above issues in sufficient detail to permit our evaluation of the adequacy of the proposals. Your response should include:

- A detailed protocol or, at a minimum, a detailed outline describing all design features of the study including sample size and justification, eligibility criteria with rationale, dosing regimens and duration, clinical assessments to be performed and their timing, and endpoints to be analyzed.*
- The proposed schedule for conducting the study/clinical trial, including all major milestones for the study/clinical trial, e.g., submission to the FDA of the finalized protocol, initiation of an animal or clinical study, completion of patient accrual, completion of the study/clinical trial, and submission of the final report, with accompanying SAS datasets and applicable revised labeling.*

Sponsor Response: The enclosed clinical protocol synopses for both the non-Caucasian study [section 2.7.6, page 66] and the drug interaction study [section 2.7.6, page 60] should provide sufficient detail to allow for FDA evaluation of study design.

Additionally, these synopses include a schedule of timelines for conducting the study, from FDA review of the proposed clinical study outline to FDA submission of data.

The total duration for the non-Caucasian study and drug interaction study is estimated to be 13.3 years and (b) (4), respectively.

The commitment to conduct these two Phase 4 studies presents us with some challenges relating to feasibility (in the case of the non-Caucasian study) (b) (4)

(b) (4) and, as a result, we would greatly appreciate the FDA's perspectives on how to proceed. We can also make ourselves available to discuss the details further with FDA, if the review team was to consider this helpful.

Reviewer's comments

The sponsor's responses for the above post marketing issues are acceptable. Please see the separate review document (DARRTS) for the post-marketing studies described in the submitted synopses.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22454	ORIG-1	GE HEALTHCARE INC	DA TSCAN

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/s/

PHILLIP B DAVIS
12/15/2009

LIBERO L MARZELLA
12/16/2009

ADDENDUM TO DIVISION DIRECTOR'S REVIEW

NDA: 22-454

Product: "DaTscan"

Sponsor: GE Healthcare

Prepared by: Dwaine Rieves, MD on September 8, 2009
Director, Division of Medical Imaging and Hematology Products

Following completion of my review document, the applicant submitted a revised package insert proposal that contained multiple important alterations (deletion of statements from the indication, new text for "Nursing Mothers," extensive revision of the Clinical Studies section) along with a publication that pertains to the "Nursing Mothers" component of the label. The extent of these revisions necessitates further clarification from the sponsor as well as justification. Indeed, some components of the sponsor's proposal appear unacceptable. Consequently, we plan to issue a Complete Response letter to address these deficiencies.

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/s/

RAFEL D RIEVES
09/08/2009

Summary Review for Regulatory Action

Date	September 1, 2009
From	Dwaine Rieves, MD
Subject	Division Director Summary Review
NDA/BLA #	22-454
Applicant Name	GE Healthcare
Date of Submission	March 6, 2009
PDUFA Goal Date	September 9, 2009
Proprietary Name / Established (USAN) Name	DaTSCAN™ Ioflupane I 123 Injection
Dosage Forms / Strength	DaTSCAN is supplied in 10-mL glass vials containing 2.5 mL of solution; each mL contains 0.07 to 0.13 mcg ioflupane, 74 MBq (2 mCi) of iodine 123 as ioflupane I 123 at calibration time along with defined excipients. The recommended dose is 111 to 185 MBq (3 to 5 mCi) administered intravenously.
Proposed Indication(s)	Datscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with clinically uncertain Parkinsonian syndromes (PS). In these patients, Datscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). Datscan is an adjunct to other diagnostic evaluations (b) (4) 
Action/Recommended Action:	Approval/Postmarketing studies to assess: 1) agreement of image results with clinical diagnoses following 3 years of follow-up among African-American patients with clinically uncertain Parkinsonian syndromes (PS) as well as 2) a study to assess the effect of dopaminergic drugs upon DaTSCAN image results.

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Phillip Davis, MD & Louis Marzella, MD, PhD (TL)
Statistical Review	Mark Levenson, PhD & Jyoti Zalkikar, PhD (TL)
Pharmacology Toxicology Review	Sunday Awe, PhD & Adebayo Lanionu, PhD (TL)
CMC Review/OBP Review	Ravindra Kasliwal, PhD & Eldon Leutzinger, PhD
Microbiology Review	Bryan Riley, PhD
Clinical Pharmacology Review	Christy John, PhD & Y. Moon Choi, PhD (TL)
DDMAC	Michelle Safarik, PA-C
DSI	Lauren Iacono-Connors, PhD & Tejashri Purohit-Sheth, MD
CDTL Review	Louis Marzella, MD, PhD
OSE/DMEPA	Denise Baugh, PharmD & Todd Bridges, PharmD (TL)
OSE/DDRE	Kathryn O'Connell, MD, PhD & Claudia Karwoski, PharmD
Pediatric and Maternal Health	Jeanine Best, MSN, RN & Karen Feibus, MD (TL)
Project Manager	James Moore, PharmD

OND=Office of New Drugs

DDMAC=Division of Drug Marketing, Advertising and Communication

OSE= Office of Surveillance and Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DSI=Division of Scientific Investigations

DSRCS=Division of Surveillance, Research, and Communication Support

CDTL=Cross-Discipline Team Leader

TL = Team Leader

CMC = chemistry, manufacturing and controls

1. Introduction:

GE Healthcare submitted a New Drug Application (NDA) to support the marketing of DaTSCAN™ (¹²³I-ioflupane), a radiopharmaceutical imaging agent with the following proposed indication:

“for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.”

During the review, multiple findings necessitated modification of the indication to that listed in the boxed header (at the top of this document). For example, data were not available to verify that DaTSCAN imaged "functional neurons." Additionally, the review disclosed multiple data limitations within the three confirmatory clinical studies. For example, Study 304 (the most informative study) was extensively modified (10 protocol amendments) that fundamentally changed its original design. The other two clinical studies (301 and 003) had even more deficits. Nevertheless, Study 304 data were particularly strong in terms of the ability of the study to compare DaTSCAN image results to a reliable clinical diagnosis (based upon 3 years of follow-up after the DaTSCAN image). Additionally, the preclinical data were indisputable in terms of

supporting the contention that DaTSCAN bound specifically to the human dopamine transporter (DaT) protein in the striatum.

The preclinical and clinical review teams supported approval of DaTSCAN. The statistical team pointed out the lack of statistical robustness within the confirmatory studies such that they regarded these studies as insufficient to support approval. The Advisory Committee voted 11 to 2 in support of a favorable risk-benefit profile for the drug. Overall, I regard the totality of data (particularly preclinical data and Study 304) as providing an acceptable risk-benefit profile for marketing. Postmarketing commitments are currently being sought to obtain data from African Americans receiving DaTSCAN and to assess the potential interference with DaTSCAN imaging by dopaminergic drugs.

The indication for DaTSCAN ultimately reflected the strength of the supplied preclinical and clinical data. This product label notes that DaTSCAN is "indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with clinically uncertain Parkinsonian syndromes (PS). In these patients, Datscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). Datscan is an adjunct to other diagnostic evaluations."

Hence, DaTSCAN may serve a useful role in the evaluation of patients with clinically uncertain PS. PS have been associated with decreased dopamine neuroactivity within the striatum, coincident with loss of dopamine-secreting (dopaminergic) neurons and DaT. The PS diseases generally consist of multiple system atrophy (MSA), progressive supranuclear palsy (PSP) and Parkinson's Disease. These conditions are, among other features, characterized by tremor. In contrast, the form of tremor identified as "Essential tremor" (ET) is not thought to be associated with loss of dopaminergic neurons and DaT. Hence, a reliable imaging test for DaT could assist the clinician in distinguishing PS from ET. The DaTSCAN clinical program verified the usefulness of the test in distinguishing PS from ET based upon a single study (Study 304) that compared baseline DaTSCAN images to clinical diagnoses after three years of follow-up. This duration of follow-up was regarded as a reliable clinical diagnostic standard, particularly since it was formed by movement disorder specialists. A supportive study (Study 003) provided additional data describing the agreement between DaTSCAN images and baseline clinical diagnoses.

2. Background:

The active drug substance in DaTSCAN is ^{123}I -ioflupane, a molecule with affinity for the DaT. DaT has been shown to be prevalent within the striatum, a portion of the brain that consists of two major parts within each cerebral hemisphere, the caudate and putamen. The presence of DaT on the surface of dopaminergic neurons assists in the recycling (uptake) of dopamine back into the neurons. Exploiting the DaT affinity of ^{123}I -ioflupane, the applicant proposed that injection of ^{123}I -ioflupane (DaTSCAN) into humans allowed visualization of the striatum on SPECT imaging and implicitly, the

detection of abnormal distribution of DaT and/or dopaminergic neurons throughout the striatum.

Diagnostic radiopharmaceuticals (such as DatSCAN) have specific regulations pertaining to their demonstration of safety and effectiveness (21 CFR part 315). The regulations note that the effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indication. The regulations provide a list of potential indication categories and the efficacy expectations for each category. For example, to obtain a "biochemical" type of indication (as the applicant generally proposed for DaTSCAN), the regulations note that, "The claim...is established by demonstrating in a defined clinical setting, reliable measurement" of the biochemical process. The regulations also note that the usefulness of the diagnostic information is determined by comparison with a reliable assessment of actual clinical status which may be provided by: (a) a diagnostic standard, (b) standards of demonstrated accuracy or (3) "established in another manner, e.g., patient follow-up." The DatSCAN clinical program generally addressed a "biochemical" type of indication in which these regulatory expectations were addressed in the following manner (Table 1):

Table 1. Regulatory Characterization of DatSCAN

Clinical Usefulness	<ul style="list-style-type: none"> • Study 304 used clinical follow-up as a comparator for DaTSCAN images; Follow-up extended over a 3 year period • Study 003 was a supportive study that compared DaTSCAN images to baseline clinical diagnoses
Reliability	<ul style="list-style-type: none"> • Data verified specificity of ioflupane binding to the human DaT (autoradiography of human brain slices with specific competition analyses) and <i>in vitro</i> binding assays of ioflupane to recombinant DaT • Study 304 also was a "defined clinical setting" that allowed a reliable estimate of agreement between DaTSCAN images and clinical diagnoses • Animal studies verified binding of radiolabeled ioflupane to striatum with displacement by DaT competitors

3. Chemistry, Manufacturing and Controls:

The Chemistry review was performed mainly by Dr. Ravindra Kasliwal. The microbiology review was performed by Dr. Bryan Riley. The reviewers verified acceptable manufacturing procedures and facility inspections also supported the approval of the application.

4. Nonclinical Pharmacology/Toxicology:

I concur with the conclusions reached by the Dr. Sunday Awe, the pharmacology/toxicology reviewer who noted that there are no outstanding pharm/tox issues that preclude approval. The pharmacology/toxicology provided some labeling recommendations which were incorporated into draft labeling. No post-marketing commitments were requested. The animal data were particularly robust in demonstrating that ioflupane binds specifically to the DaT within the striatum of animals. Autoradiography of human brain slices verified the specificity of ioflupane for DaT within the human brain.

5. Clinical Pharmacology/Biopharmaceutics:

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval. The reviewer provided some recommendations for labeling which were incorporated into the draft labeling text. No outstanding issues were identified and no post-marketing commitments were requested.

The reviewer provided specific recommendations for certain pharmacology information within the labeling and these items were incorporated into the final labeling.

6. Clinical Microbiology:

The microbiology reviewer recommended approval and I concur with his findings..

7. Clinical/Statistical-Efficacy:

Dr. Phillip Davis provided the main clinical review and Dr. Mark Levenson provided the main statistical review and below I summarize the major clinical data.

Overall, three major clinical confirmatory clinical studies were submitted in the application, Studies 003, 304 and 301. Study 301 examined image results among patients with dementia while the other two studies examined patients with tremor. A supportive study (the Walker Study) was also supplied; this study compared DaTSCAN images to autopsy diagnoses of dementia. Hence, the development program focused upon two major areas: dementia and clinically uncertain PS.

The basis for potential use of DaTSCAN in PS was described in the introduction to this document. The basis for the potential use of DaTSCAN in dementia relates to the observation that Dementia with Lewy Bodies (a specific type of dementia) has been associated with loss of DaT while other types of dementia (e.g., Alzheimer's) generally are not associated with DaT loss.

a. Evaluation of patients with tremor:

The safety and efficacy of Datscan were evaluated in two multicenter, single-arm studies (Study 304 and Study 003) that evaluated 287 adult patients with tremor. In the studies,

DaTSCAN image outcomes were compared to a clinical diagnostic standard of "PS" or "non-PS". The clinical diagnostic standard for "PS" consisted of the following diagnoses: Parkinson's disease, multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). These three conditions have been associated with dopaminergic neurodegeneration and DaTSCAN imaging was not designed to distinguish among the conditions. The reference clinical diagnostic standard for "non-PS" consisted of an essential tremor (ET) diagnosis or other non-PS diagnosis. Both studies excluded subjects with concomitant medications known or suspected of interacting with striatal uptake of DaTSCAN. Three to 6 hours after DaTSCAN administration, subjects underwent SPECT imaging with a variety of multi-headed cameras or a multi-detector single-slice systems.

DaTSCAN images were evaluated by readers blinded to clinical information. Study 304 readers had no other role in patient assessment; Study 003 readers included site investigators. The clinical diagnostic standards were the clinical diagnoses established by a consensus panel of movement disorder specialists that evaluated data inclusive through 36 months of follow-up (Study 304) or the investigator-determined baseline clinical diagnosis (Study 003). Study 304 consisted of patients with early features of Parkinsonism; patients with features suggestive of MSA or PSP were excluded. Study 003 consisted of patients with clinically established diagnosis of PS (Parkinson's disease, MSA, PSP) or ET.

Table 4 shows the positive percent agreement and negative percent agreement of the Datscan image results with the reference clinical diagnostic standard. Positive percent agreement represents the percent of patients with abnormal Datscan images among all the patients with a clinical diagnostic reference standard of PS. The negative percent agreement represents the percent of patients with normal Datscan images among the patients with a non-PS clinical diagnostic reference standard.

Table 2. Positive and Negative Percent Agreements for Studies 1 and 2

Reader	Positive percent agreement (95 % CI) (% patients with an abnormal Datscan image among patients with PS)	Negative percent agreement (95 % CI) (% patients with a normal Datscan image among patients with non-PS)
Study 1 (patients with early signs and/or symptoms of PS)		
Reader A, n = 102	78 (66, 87)	97 (83, 100)
Reader B, n = 99	78 (66, 87)	97 (83, 100)
Reader C, n = 101	79 (67, 88)	97 (83, 100)
Study 2 (patients with established diagnoses of PS or ET)		
Reader A, n = 185	93 (88, 97)	96 (81, 100)
Reader B, n = 185	97 (93, 99)	74 (54, 89)
Reader C, n = 185	96 (92, 99)	85 (66, 96)
Reader D, n = 185	92 (87, 96)	93 (76, 99)
Reader E, n = 185	94 (90, 97)	93 (76, 99)

b. Evaluation of patients with dementia:

Study 301 evaluated patients with various forms of dementia. The study compared DaTSCAN images to baseline clinical diagnoses, as well as clinical diagnoses after one year of follow-up. (b) (4)

The "Walker" study compared dementia diagnoses from autopsy histopathology to DaTSCAN images made many months prior to death. Within the "Walker" Study, clinical diagnoses were incorrect in 9/22 patients and DaTSCAN findings were incorrect in 4/22 patients. The small sample size as well as limitations within the histopathology diagnostic criteria were regarded by the FDA review team as important limitations to these data.

(b) (4)

8. Safety:

The most notable safety findings pertain to the postmarketing experience. DaTSCAN has been marketed in Europe since 2000. During this time hypersensitivity reactions have uncommonly been reported. These reactions generally consisted of rash and pruritus and either resolved spontaneously or following the administration of corticosteroids and anti-

histamines. The risk for hypersensitivity reactions was cited as a warning in the label. No serious adverse reactions were observed in the clinical trials and adverse reactions were uncommon (<1% of patients). Adverse reactions consisted of headache, nausea, vertigo, dry mouth or dizziness. These reactions were of mild to moderate severity.

The risk for thyroid uptake of radioactive iodine was highlighted as a warning within the DaTSCAN label and the label includes direction for administration of a thyroid uptake blocking agent to prevent thyroid accumulation of radioactive iodine.

The review team regarded labeling as a sufficient measure for risk management. No risk evaluation and mitigation strategy was regarded as necessary, a conclusion supported by the OSE/DRISK review.

Post-marketing Requirements (PMR): none

Post-marketing Commitments: at the present time we are negotiating studies in African Americans (almost all patients in clinical trials were Caucasian) and studies to assess the impact of dopaminergic drugs upon DaTSCAN imaging.

9. Advisory Committee Meeting:

This application was presented to the Peripheral and Central Nervous System Advisory Committee on August 11, 2009. The committee voted (11 to 2) to conclude that the presented data represented a favorable risk to benefit profile for DaTSCAN.

10. Pediatrics:

Clinically uncertain PS was regarded as not applicable to the pediatric patient population and pediatric studies were waived.

11. Other Relevant Regulatory Issues:

Overall, the review team regarded the supplied data as supporting a favorable risk-benefit finding. The drug was associated with relatively few safety concerns and no unique risk management activities were regarded as necessary. In other matters, the FDA inspection of clinical sites disclosed no remarkable findings; financial disclosure expectations have been met.

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/s/

RAFEL D RIEVES
09/02/2009

Clinical Review
Phillip Davis, MD
NDA 22454
Ioflupane I 123, DaTSCAN

CLINICAL REVIEW

Application Type NDA
Application Number(s) 022454
Priority or Standard P

Submit Date(s) March 6, 2009
Received Date(s) March 9, 2009
PDUFA Goal Date September 9, 2009
Division / Office September 8, 2009/September 2, 2009

Reviewer Name(s) Phillip Davis, MD
Review Completion Date August 21, 2009

Established Name Ioflupane I 123
(Proposed) Trade Name DaTSCAN
Therapeutic Class Diagnostic Radiopharmaceutical
Applicant GE Healthcare

Formulation(s) Sterile aqueous solution 2mCi123I /ml
in 2.5 ml vial for intravenous injection
Dosing Regimen Single dose 3-5 mCi IV
Indication(s) Detecting loss of functional nigrostriatal
dopaminergic neurons by single photon
emission computed tomography
Intended Population(s) Patients presenting with symptoms and
signs suggestive of dopaminergic
neurodegeneration

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Clinical Review
Phillip Davis, MD
NDA 22454
loflupane I 123, DaTSCAN

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of the NDA for Datscan (ioflupane I 123) for the indication of visualization of the dopamine transporter (DaT) distribution within the striatum by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs of Parkinsonism. This recommendation is based on review of the pre-clinical data and clinical data supporting the claim that Datscan binds to the DaT protein in the striatum, combined with the review of the two phase 3 studies evaluating the effectiveness of Datscan in patients with Parkinsonism. This approval is also based upon review of the safety data submitted from the European clinical development program and the post-marketing data.

1.2 Risk Benefit Assessment

This radiopharmaceutical has an acceptable risk benefit assessment based on the following qualities:

- Single dose (3-5 millicuries, < 0.325 micrograms) by intravenous administration
- Limited indication (Parkinsonism subjects)
- Limited patient population (adult patients)
- > ^{(b) (4)} patients exposed in the European market since 2000 without reports of serious adverse events or deaths related to study drug.
- Datscan SPECT imaging provides additional information currently unavailable to clinicians outside of research settings in evaluating subjects with Parkinsonism.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

None are needed.

1.4 Recommendations for Post-market Requirements and Commitments

The applicant should design and perform the following:

- A phase 4 study designed to assess the effect of anti-parkinsonian medications (at least carbidopa/levodopa and dopamine agonists) on Datscan performance characteristics.

2 Introduction and Regulatory Background

2.1 Product Information

Datscan is a radiopharmaceutical containing Iodine-123 labeled Ioflupane (ioflupane I 123 or [¹²³I]FP-CIT), a radioisotope-labeled cocaine analog, which binds to the dopaminergic transporter (DaT) protein in the brain. Datscan is administered by intravenous route, and the original submitted indication was for *detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.*

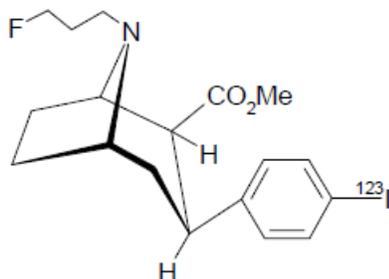
The revised indication, proposed by the Agency in the briefing document for the August 11, 2009 Peripheral and Central Nervous System Drugs Advisory Committee Meeting is *for visualization of the dopamine transporter (DaT) distribution within the striatum by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.* This indication was accepted by the sponsor and represents the current, proposed indication for Datscan.

(b) (4)

The Datscan final drug product contains ¹²³I-ioflupane, ioflupane, ethanol and sodium acetate (b) (4). The drug product is delivered as a sterile solution in 2.5 ml vials ready for intravenous injection.

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Structural Formula:



Molecular Formula: $C_{18}H_{23}F [^{123}I] NO_2$

Relative Molecular Mass: 427.29 (for the radioactive compound)

2.2 Tables of Currently Available Diagnostic Agents for Proposed Indication

Currently, there are no approved imaging agents in the U.S. for visualization of the dopamine transporter (DaT) distribution within the striatum.

2.3 Availability of Proposed Active Ingredient in the United States

This drug product is a new molecular entity and is not currently marketed in the U.S.

If approved, ^{123}I -ioflupane will be manufactured by GE Healthcare at the GE Arlington Heights facility in Illinois. The manufacturing of ^{123}I -ioflupane (b) (4)

materials used for the manufacturing of ^{123}I -ioflupane are controlled and released according to GE Healthcare specifications prior to use.

2.4 Important Safety Issues with Consideration to Related Drugs

Datscan contains the compound ioflupane, which is a cocaine analogue, labeled with the radioactive isotope, Iodine-123. Relevant safety issues include the presence or absence of pharmacologic activity following administration of the cocaine analog contained in DaTSCAN.

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As with all radiopharmaceuticals, radiation safety concerns are present secondary to the emission of gamma radiation (photon energy of 159 KeV) by the Iodine-123 radioisotope contained in Datscan. The reported effective dose of 3.94 milliseverts for a 5 mCi dose of Datscan represents an acceptable level of radiation exposure compared to guidelines for radiation workers, and is at the lower range of radiation effective dose for nuclear medicine imaging procedures.

It is not known whether Datscan is excreted into human milk. However, free Iodine-123 is secreted in human breast milk. Therefore, a decision regarding interrupting nursing following Datscan administration in order to minimized risks to nursing infants should be made by the patient's physician.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

DaTSCAN is approved in Europe and marketed in 32 countries. The sponsor relies solely on data from the European clinical development program, along with data from one ongoing investigator-initiated study in the United Kingdom as evidence of efficacy to support U.S approval. Pivotal phase 3 study issues regarding primary efficacy variable (sensitivity and specificity), statistical evaluation, and patient population were only discussed with the sponsor following completion of the European development plan.

In 2008, the agency held two face-to-face (Type C) sponsor meetings (1/31/2008 and 8/20/2008) regarding the sponsor's intention of seeking U.S approval of DaTSCAN. During the 8/20/2008 meeting, the sponsor stated an NDA for Datscan would be submitted based on existing data from the completed European development program. The Agency did not agree with this approach and listed a number of concerns regarding the studies performed for the European clinical development program. These concerns included lack of a validated standard of truth (SOT) for all the phase 3 studies performed by the sponsor, as well as a concern regarding the study reports selected to be submitted in the NDA as "principal studies to support US registration". The Agency commented that these principal studies may "not provide the primary basis for determining whether there is substantial evidence to support the claim of effectiveness of Datscan in detecting loss of functional nigrostriatal dopaminergic neurons, especially as it relates to its association with Parkinson's disease (PD)". Additionally, the Agency stated that the development program in the population of patients with Dementia with Lewy bodies (DLB) "appears to be somewhat more robust".

The Agency recommended a new phase 3 study "with a pre-specified clinically meaningful primary endpoint which would evaluate the diagnostic performance of your agent in the patient population of intended use, with the SOT consisting of a clinical diagnosis by a movement disorder specialist, and with Datscan images being evaluated by the properly conducted blind reads". The Agency also recommended to "involve a

representative number of US sites in such a study". The sponsor did not conduct any additional phase 3 studies as recommended in this last meeting with the Agency.

2.6 Other Relevant Background Information

In the European market (32 countries), the approved indication for Datscan is more specific than the proposed U.S. indication. The primary European indication is for use in the diagnosis of subjects with clinically uncertain Parkinsonian syndromes (PS) to help differentiate them from subjects with essential tremor (ET), and for use in the diagnosis of subjects with clinically uncertain dementia with Lewy bodies (DLB) to help differentiate them from subjects with other types of dementia, such as Alzheimer's Disease (AD). GE Healthcare has been manufacturing Datscan at the Eindhoven, The Netherlands facility since 2000 in compliance with European cGMPs. The European clinical development program data have been re-analyzed and re-reported for this NDA submission to support the proposed indication.

The dementia with Lewy bodies consortium published revised criteria for the clinical and pathologic diagnosis of DLB in 2005¹. As part of the criteria for the clinical diagnosis of DLB, the criteria include "Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging" as a suggestive feature of DLB. The UK Brain Bank diagnostic criteria for the diagnosis of parkinsonian syndrome does not include imaging of the dopamine transporter as part of the supportive features for diagnosis.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The division consulted DSI regarding site inspections for this NDA. The pivotal studies utilized multiple study sites throughout Europe and the UK. Table 1 provides the study sites selected for inspection based upon these reasons:

- studies considered most important in demonstrating efficacy and safety claims (studies PDT-301 and PDT-304)
- (b) (4)
study sites (site #23, study PDT-301)
- number of patients enrolled at these site(s) exceeded the number of patients enrolled at all other study sites for the study of interest (site # 26, study PDT-301)
- imaging review centers for studies PDT-301 and PDT-304 were selected to investigate conformance with the blinded image evaluation protocol.

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Table 1: Description of studies and study sites selected for DSI inspections

Site Name and Address	Report # / Protocol #	Number of subjects	Indication
Site # 23 Southampton Memory Assessment & Research Center	Study PDT-301 An open-label, phase 3, clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN, in subjects with dementia with lewy bodies.	18 enrolled/ 17 received study drug	(b) (4)
Site # 26 Neurologia 2, Spedali Civili di Brescia	Study PDT-301 An open-label, phase 3, clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN, in subjects with dementia with lewy bodies.	29 enrolled/ 25 given study drug	Site # 26 enrolled more patients than any other center for study PDT301.
(b) (4)	Study PDT-301	235 evaluable for efficacy (PP)	Inspect (b) (4) for adherence to blinded image evaluation protocol.
(b) (4)	Study PDT-304	102 evaluable for efficacy (PP)	Inspect (b) (4) for adherence to blinded image evaluation protocol.

The DSI report revealed no major deficiencies that could compromise the integrity of the data.

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3.2 Compliance with Good Clinical Practices

In the application, GE Healthcare states the pivotal studies for safety and efficacy 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 Harmonization, and applicable national and local laws and regulations (e.g., Code of Federal Regulations Parts 50, 54, 56, 312, and 314). At each participating study site, the protocol and all amendments were approved by an Institutional Review Board. Written informed consent was obtained from each subject before any procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained. Subjects were informed that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.” The applicant also states that “it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

GE Healthcare pursued financial disclosure for all phase 3 studies submitted to support the efficacy of Datscan for the proposed indication, with the exception of study 003. This study was completed prior to 2/2/1999, making it exempt from financial disclosure requirements as stated in the March 20, 2001 FDA Guidance for Industry: Financial Disclosure by Clinical Investigators.

The applicant submitted a list of clinical investigators who participated in studies 301, 304 and the Walker study. Review of the financial disclosure documents reveals missing information for numerous investigators from study 301 (167 missing investigator disclosures), study 304 (26 missing investigator disclosures), and the Walker study (4 missing investigator disclosures). Reasons for inability to obtain financial disclosure from these investigators included “no longer at site”, “could not obtain”, “no response”, “left hospital”, “left the department”, and “not known at hospital”.

Additionally, five investigators who participated in sponsor-initiated phase 3-4 studies disclosed financial interests and/or arrangements with the sponsor. An investigator for study 301, site number (b) (6) received two grants (25,000 DM (b) (6) and 23,500 Euro on (b) (6) to fund ongoing research. His site recruited 1% of the enrolled subjects for study 301. The applicant stated the investigator’s research grants did not influence study outcomes, and the results from this site were consistent with results seen at other study sites for overall study outcomes.

An investigator for studies 301 and 304, site numbers (b) (6) respectively, works as a consultant for GE Healthcare, for which he receives annual monetary compensation (15,000 to 28,000 pounds annually). GE states that consultancy fees paid to the investigator did not influence the outcomes of these studies for these reasons: 1) 4-5% of the enrolled subjects in studies 301 and 304 were recruited at the

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site of this investigator, and 2) Results from these sites were consistent with results at other study sites and for the overall study outcome for studies 301 and 304.

An investigator for study 301, site number (b) (6), reported receipt of a research grant on (b) (6) (23,500 Euro). The applicant states this grant did not influence study outcomes because: 1) This site recruited 1% of the enrolled subjects, and 2) Results from this site were consistent with results observed at other sites and for overall study outcomes.

Another investigator for study 301 at site number (b) (6) received two grants to fund ongoing research (25,000 DM received (b) (6) & 23,500 Euro received (b) (6)). The applicant states these grants did not influence study outcomes for these reasons: 1) This site recruited 1% of the enrolled subjects, and 2) The results from this site were consistent with results seen at other study centers and for the overall study outcomes.

The principal investigator for studies 301 and 304, site numbers (b) (6) respectively, reported receipt of research material (approximate value of \$25,000) provided by the sponsor. The sponsor states that this research material did not influence study outcomes for these reasons: 1) These sites recruited 1% and 17% of the enrolled subjects for studies 301 and 304, respectively. 2) The results from these sites were consistent with results observed at other study sites and for overall outcomes for studies 301 and 304.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review did not report issues that might affect efficacy or safety.

4.2 Clinical Microbiology

No issues to report.

4.3 Preclinical Pharmacology/Toxicology

The summary of the preclinical pharmacology/toxicology review states the sponsor provided adequate preclinical data on the safety of Datscan for the proposed indication, and the product was recommended for approval from the pharm/tox perspective.

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The data showed high affinity and selectivity of Datscan for the Dat protein and this could provide in vivo images as a measure of the Dat protein distribution in the striatum. Datscan metabolites did not cross the blood brain barrier and no CNS pharmacological effect is expected following the metabolism of this compound. Due to similarity in the pharmacology of FP-CIT to that of other DaT ligands like cocaine, hyperactivity and stereotypic behavior was observed at high doses.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Datscan ($[^{123}\text{I}]$ FP-CIT) is a radiolabeled cocaine analog which binds reversibly to the dopamine transporter protein (DaT) found in the axon terminals (located in striatum) of pre-synaptic nigrostriatal neurons. Nigrostriatal neuron cell bodies are located in the substantia nigra pars compacta region of the brain. These neurons have axons which project to and terminate in the striatum (putamen and caudate nucleus). Signals are transmitted from nigrostriatal neurons to striatal neurons by release of dopamine into the synapse, which binds to the post-synaptic striatal neurons. DaT proteins terminate neuronal signaling between nigrostriatal neurons and striatal neurons by participating in dopamine reuptake into the pre-synaptic nigrostriatal neurons, which prevents continuous neuronal firing.

Datscan is used as an indirect method to detect the loss of nigrostriatal neurons. The DaT protein is used as a marker for nigrostriatal neurons, and loss of these neurons will result in loss of the DaT protein. With nigrostriatal neuron loss, there should be less or no visualization of Datscan (by SPECT) in the striatum compared to individuals with any age-related changes.

4.4.2 Pharmacodynamics

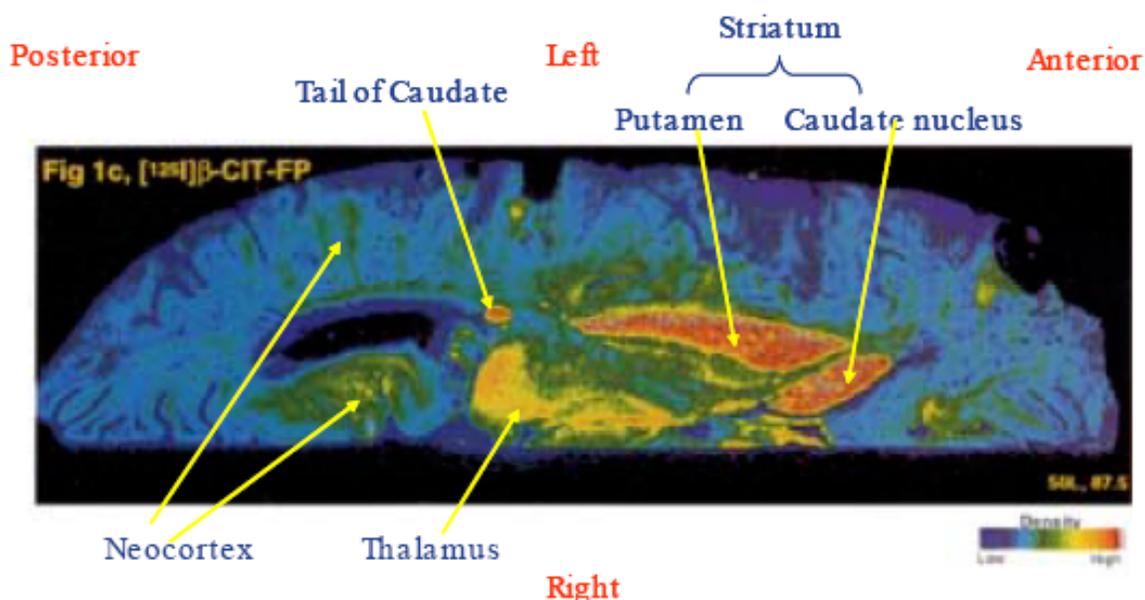
Pharmacological effects are not observed in humans following the intravenous administration of the proposed dose of ≤ 0.325 micrograms. Estimates from phase 2 studies indicate that Datscan occupies less than 1% of DaT proteins in the brain, with no expected pharmacological effect at this level of occupancy.

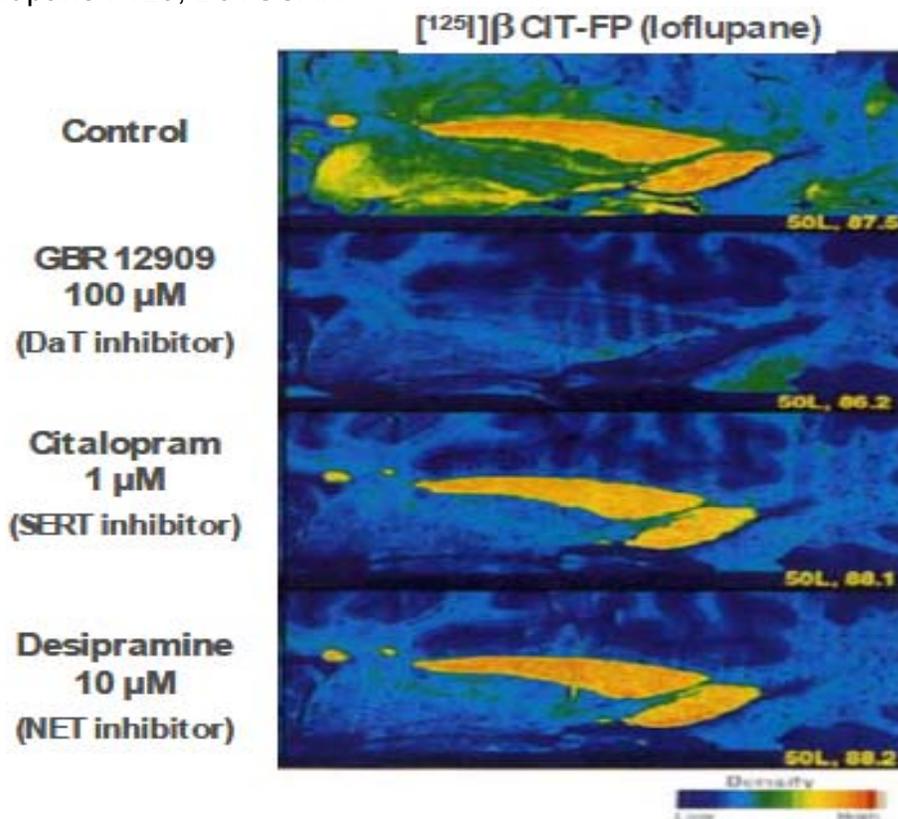
The affinity of FP-CIT for the human dopamine transporter (DaT) has been evaluated by the applicant in competitive binding studies at test agent doses between 0.1 nM and 100 μM . FP-CIT inhibited binding at the human recombinant dopamine transporter with a K_i of 0.62 nM and an IC_{50} of 0.70 nM. FP-CIT showed a 3- to 4-fold selectivity for the dopamine transporter over the serotonin transporter. Table 2 shows human recombinant targets where FP-CIT shows significant binding.

Table 2: Inhibition of Ligand Binding by FP-CIT (non radioactive)

Target	% inhibition (at conc.)	IC ₅₀	Ratio of target:DA transport IC ₅₀	K _i	Ratio of target:DA transport K _i
DaT	52 (1 nM)	701 pM	1	623 pM	1
Adrenergic NET	75 (1 μM)	229 nM	327	73 nM	117
SERT	79 (10 nM)	2.9 nM	4.14	1.9 nM	3.05

Literature reports of autoradiography of post-mortem human brain sections exposed to the radioligand have been performed in the presence and absence of competitive inhibitors in order to determine the selectivity and affinity of [¹²⁵I]-FP-CIT binding.





The above figures show autoradiograms obtained with [¹²⁵I]FP-CIT. To study the specificity of the binding of [¹²⁵I]-FP-CIT in post mortem human brain, competition studies with citalopram (SERT-specific ligand), desipramine (NET-specific ligand) and GBR 12909 (DaT-specific ligand) were carried out by Gunther *et al.* Citalopram reduced binding in the neocortex and thalamus with only minor effects in the striatum. This indicates that the binding in the cortex and thalamus is mainly to SERT. The NET inhibitor, desipramine, showed no effect on the level of striatal binding but reduced extrastriatal binding by 60 to 85%. Binding to all regions was abolished when including a high concentration of the predominantly DaT inhibitor, GBR 12909, leaving a low level of nonspecific binding. A concentration of 1 μM GBR 12909 reduced labeling in the caudate nucleus and putamen by approximately 50%. The data indicate selectivity of binding for the pre-synaptic DaT rather than post-synaptic dopamine receptors. The distribution of radioactivity within the brain sections is consistent with the selective affinity of the [¹²⁵I]-FP-CIT for the DaT.^{7,9}

Clinical Pharmacology Reviewer’s comments/conclusions:

The pharmacodynamic data show that Datscan has high affinity and some selectivity for DaT. The presence of different regional transporter densities supports the notion that a degree of contrast between DaT-rich and -deficient regions is achievable in normal individuals. Human physiology and pathology data show that DaT is located in dopaminergic neurons and that loss of these neurons is one characteristic of Parkinsonian disorders. These data support the use of Datscan as a qualitative marker of dopaminergic neuronal density.

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4.4.3 Pharmacokinetics

Phase 1 studies of Datscan revealed approximately 96% clearance from the blood at 15 minutes post injection, decreasing to 1% of the injected dose at 48 hours. Brain uptake was 7% of the injected Datscan dose, with 30% of brain uptake located in the striatum. The ratio of binding in the striatum to the occipital regions was approximately 3 to 1. Imaging of Datscan brain uptake is best performed between 3-6 hours post-administration, when binding levels are stable. Datscan is primarily excreted in the urine, with approximately 60% of injected dose voided by 48 hours.

In a phase 2 study, the highest absorbed radiation dose following Datscan administration was seen in the urinary bladder wall (0.054 mGy/MBq), followed by the lungs (0.043 mGy/MBq), lower large intestine (0.042 mGy/MBq) and the upper large intestine (0.038 mGy/MBq). Dosimetry estimates using OLINDA software indicate the total effective dose to be approximately 3.94 mSV for an administered activity of 5 mCi.

There have been no human studies to investigate Datscan drug interactions. Drug interactions with Datscan are considered possible based on the mechanism of action of reversible binding to the DaT protein. Drugs which bind the DaT protein could theoretically block or reverse Datscan binding to the DaT ligand. The applicant provides a list of drugs with potential to interfere with DaTSCAN binding, these include: benztropine (an anti-cholinergic tropane); cocaine (a tropane); mazindol, amphetamine, phentermine and methylphenidate (sympathomimetics); bupropion (an atypical anti-depressant used to treat nicotine addiction); and sertraline (and possibly other serotonin re-uptake inhibitors). Drugs with the ability to alter Datscan binding could possibly affect the diagnostic accuracy of Datscan SPECT imaging.

Reviewer's comments:

Assuming interference of Datscan binding occurs with certain medications, the most plausible consequence would be reduced or absent Datscan signal in the striatum. With reduced Datscan signal in the striatum, the most likely result would be increased false positive test results. Lack of clinical data on Datscan drug interactions presents a concern for use of Datscan imaging in patients taking the above mentioned medications, as well as for patients taking dopaminergic medications for Parkinsonism.

Previous studies of related compounds (beta-CIT) have shown disagreement between clinical status and Datscan image results in patients receiving dopaminergic medications to treat Parkinson's disease at the time of Datscan SPECT imaging.^{6,10} Future clinical studies will be needed to assess the effects of these medications on Datscan SPECT imaging results. At minimum, the sponsor may need to conduct a study designed to assess the effect of anti-parkinsonian medications (at least carbidopa/levodopa and dopamine agonists) on image results.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 3: Studies included for efficacy and safety evaluation

Study Number, Number of study centers, Location(s)	Study period, N, dosing	Design, Standard of truth (SOT), Image analysis method (IAM)	Primary endpoints
CY95.FP.I	N=12 healthy volunteers (HV) Single 3 mCi dose	Phase 1, single center, single group, open label, non-randomized, non-controlled PK and safety study of Datscan	Safety
CY96.FP.II	N=30 (10 HV, 20 PD patients) Single 3 mCi dose	Phase 2, single center, parallel group, open label, non-randomized, non-controlled study of Datscan uptake in various brain regions and assess safety and tolerability of Datscan	Safety
PDT02005	N=51 (26 PS patients, 25 non-PS patients) Single 3-5 mCi dose	Phase 2, non-comparative, open-label, non-randomized, non-controlled study of Datscan in differentiating between subjects with vascular Parkinsonism, cerebrovascular disease and HV	safety and activity
Phase 3 and 4			
Study 301 (PDT301) 40 centers in Europe participated	12/21/2003 to 6/28/2006 N=326 Single 3-5 mCi dose	Multi-center, open-label, non-randomized study SOT = expert clinical diagnosis at baseline as established by consensus panel of DLB experts IAM = BIE at image review center (b) (4)	Sensitivity and specificity of Datscan images in differentiating between DLB and non-DLB dementia.
Study 304 (PDT304) 10 centers in	1/18/1999 to 6/28/2005 N= 179	Multi-center, open-label, non-randomized study SOT = consensus	Sensitivity and specificity of Datscan images in

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Europe participated.	3 totals doses: 3-5 mCi at 3 separate time points (T=0, T=18, T=36)	diagnosis by 2 movement disorder specialists (MDS) by taped video assessment (T= 36 months), IAM = BIE by 3 independent readers at (b) (4)	differentiating between early Parkinsonism and other causes of tremor and healthy volunteers
Study 003 (DP008-003) 6 centers in Europe	8/25/1997 to 2/24/1998 N=224 Single 3 – 5 mCi dose	Multi-center, open-label, non-randomized study SOT = on-site clinical diagnosis at baseline by consensus criteria IAM = On site evaluation by study investigators (Central, BIE also performed for 2° efficacy analysis)	Sensitivity and specificity of DaTSCAN images in confirming the documented, clinical diagnosis of PD, MSA, PSP or ET
PDT03007 (All subjects previously participated in Study 003)	1/18/2000 to 10/27/2000 N=31 (8 HV, 20 PS patients, 3 ET patients) Single 3-5 mCi dose	Phase 3, multi-center, open label, non-randomized, non-controlled study to investigate change in Datscan uptake after 2 years	Semi-quantitative striatal uptake of Datscan
PDT408	N= 120 PS patients	Multi-center, open label, non-randomized, non-controlled study to assess the impact of Datscan imaging on patient diagnosis, physician confidence and management	Proportion of subjects in which clinical diagnosis of PS can be supported or excluded after Datscan imaging
Walker Study 12 investigators at one study site in the UK participated. (all image interpretations performed at (b) (4))	6/1996 to 12/1999, (autopsy phase ongoing) 22 subjects with available SOT assessment Single 3 mCi dose	Investigator-initiated, single-center, open-label, non-randomized, exploratory study SOT= neuro-pathological diagnosis at autopsy IAM = BIE performed according to 3 point qualitative scale by 3 readers in CP. A semi-quantitative analysis was performed by 1 blinded reader.	To determine: 1. Sensitivity and specificity of Datscan images in confirming diagnoses of DLB and AD. 2. Semi-quantitative analysis of Datscan uptake

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5.2 Review Strategy

Emphasis was concentrated on the review of Datscan pre-clinical and clinical pharmacology data in order to investigate the sponsor's claim that Datscan binds to the DaT protein with some specificity and selectivity. In addition, literature reports of autoradiography performed on human brain slices and in-vitro studies of ioflupane binding to human recombinant transporters (DaT, SERT, NET) allowed evaluation of the affinity and selectivity of Datscan for the human DaT protein^{7,9}. Of note, similar data was not presented in studies of human brain tissue from subjects with disease pathology analogous to subjects included in the proposed indication.

For the efficacy evaluation (demonstration of clinical usefulness, reliability and accuracy in a defined clinical setting), this review concentrates on the 4 studies described in table 3 and detailed in tables 5 through 8. The review will focus on the original primary endpoints of sensitivity and specificity of Datscan in differentiating between PS and non-PS movement disorders and between DLB and non-DLB dementia.

For the review of safety, information was evaluated from one phase 1 study (CY95.FP.I), two phase 2 studies (CY96.FP.II & PDT02005), six phase 3 studies (PDT301, PDT304, DP008-003, PDT03007, PDT408 and Walker). The total number of patients included in the safety analysis was 924 subjects.

5.3 Discussion of Individual Efficacy Studies/Clinical Trials

Overview

The applicant relies solely on data from the European clinical development program (studies PDT301, PDT304 and DP008-003), along with data from one ongoing investigator-initiated study (Walker study) in the United Kingdom to support efficacy claims. Prior to initiation of these studies, there were no agreements with the Agency regarding study designs and methods for pursuing U.S. registration. There were modifications of study objectives and statistical analyses to generate the U.S. clinical study reports from the European clinical study reports. The applicant performed post hoc analyses of each of these studies evaluating diagnostic performance of Datscan in the creation of the U.S. study reports.

All applicant sponsored phase 3 studies were multicenter, open-label, non-randomized clinical studies, originally designed to assess the diagnostic performance and safety of Datscan in subjects with dementia and/or movement disorders. The primary objectives of these studies as presented in the revised U.S. study reports were to determine the sensitivity and specificity of visual interpretations of Datscan SPECT images in detecting or excluding a striatal dopaminergic deficit (SDD). Visual assessments of Datscan images were compared to the clinical diagnosis (SOT) to determine sensitivity and specificity. With exception of the Walker study, the sponsor has utilized the clinical

diagnosis (SOT) as a surrogate for pathology in order to detect loss of functional nigrostriatal dopaminergic neurons, also known as a SDD. The sponsor does this by assuming presence of a SDD in subjects diagnosed with any of the Parkinsonian syndromes (IPD, PSP, MSA) and DLB, and assuming absence of a SDD in subjects clinically diagnosed with ET, AD and healthy volunteers.

Detailed imaging review charters were not provided for the phase 3 studies, but image acquisition and interpretation methods were briefly described in the study reports. Only one study, PDT301, had pre-defined statistical thresholds for success. Studies PDT304 and DP008-003 had pre-defined statistical analysis plans, but no pre-defined statistical thresholds. Of note, the clinical diagnoses were determined using different methods and by physicians with different areas of specialty for each study. Additionally, different blinding methods for image readers were used for each study.

Table 4 illustrates the basic revisions performed by the applicant to create U.S clinical study reports from the original European clinical study reports for studies considered pivotal in supporting efficacy and safety claims. For the remainder of this review, Study PDT-301 will be referred to as 301, Study PDT-304 will be referred to as 304, and Study DP008-003 will be referred to as 003.

Table 4: Comparison of European and U.S. study reports.

Study	301	304	003	Walker
Population	Dementia subjects (possible DLB, AD, VaD)	Early Parkinsonism subjects (PD and ET) and healthy volunteers	Subjects with documented clinical diagnosis of PD, MSA, PSP or ET and healthy volunteers	Subjects with clinical diagnosis of DLB, AD, or PD, and healthy volunteers
Pre-specified primary endpoints	Sensitivity (Sens) and specificity (Spec) in differentiating between “probable”-DLB and non-DLB	PPV, NPV, Sens, Spec, & Accuracy of DaTSCAN image assessments	Sens and Spec of DaTSCAN striatal uptake	Sens and Spec for visual image assessment and clinical diagnosis, SensQuantitative DaTSCAN uptake ratios
Primary endpoints for U.S. study report	Sensitivity and specificity for detecting or excluding a SDD	Sensitivity and specificity for detecting or excluding a SDD	Sensitivity and specificity of DaTSCAN images in differentiating between PS and non-PS subjects	Sensitivity and specificity of DaTSCAN images in confirming diagnoses of DLB, AD, PD and in healthy controls

Individual Studies

Table 5: Study 301

Study 301	
Design	Phase 3, multi-center (40 centers), open-label, non-randomized single dose study to determine the sensitivity and specificity of Datscan imaging in differentiating between subjects with Dementia with lewy bodies (DLB) and other forms of dementia (AD, VaD)
Protocol date (Original)	6/17/2003
Amendments to protocol	10/02/2003, 04/08/2004, 01/11/2005, 04/21/2005
Statistical plan date	Not stated
Study dates	11/21/2003 to 6/28/2006
Inclusion criteria	Male or female 55 to 90 years of age Clinical diagnosis of dementia according to DSM-IV and: 1. ICC probable or possible for DLB 2. NINCDS-ADRDA for AD, or 3. NINDS-AIREN for VaD, and: 4. Mini mental state examination score ≥ 10
Main exclusion criteria	1. Diagnosis of PD 2. Pregnancy 3. Past cerebral infarction in region of basal ganglia 4. Severe depression 5. Normal pressure hydrocephalus 6. Interfering medications (does not include dopamine agonists and antagonists)
Primary endpoints	Sensitivity and specificity of DaTSCAN visual assessment (BIE) in differentiation between patients with "Probable" DLB

	versus non-DLB dementia (using baseline CP clinical diagnosis as SOT).
Secondary endpoints	<ol style="list-style-type: none"> 1. Re-evaluation of the primary and secondary efficacy endpoints via the 12 month re-assessment of the clinical diagnosis 2. Accuracy, PPV, NPV based on the dichotomous visual read (BIE) compared to the clinical diagnosis given by an independent CP from a documented assessment. 3. Assessment of Datscan ability to increase investigator performance and confidence in differential diagnosis of DLB and other types of dementia and to assess clinical usefulness of management decisions for subjects with DLB. The accuracy and sens/spec of the on-site investigator's baseline diagnosis will be compared to those of the investigator's post- Datscan diagnosis. 4. Summary of the proportions of abnormal/normal Datscan SPECT visual reads (BIE) in relation to the groups of probable DLB, possible DLB, and non-DLB 5. Semi-quantitative analysis of Datscan images: comparison of striatal uptake ratios between the 3 groups of probable, possible and non-DLB dementia
Safety endpoints	<p>Proportion of subjects with 1 or more treatment-emergent AEs; Any clinically significant changes from baseline in clinical assessments (PE, EKG, vital signs, labs);</p> <p>Safety evaluation was not part of the 12-month follow-up</p>
Standard of truth	Clinical diagnosis by consensus panel (3 DLB experts) at T=0 (primary efficacy measurement) & reassessment at T=12 months
Statistical thresholds for success	Sensitivity – 65%, Specificity – 73%
Clinical diagnosis method	Established by an independent, off-site

	<p>consensus panel of 3 DLB experts by review (no physical examination) of all available clinical data (laboratory and prior imaging results, excluding Datscan imaging results) from the study site, including on-site investigator's clinical diagnosis, and based on the following diagnostic criteria:</p> <p>Alzheimer's Disease: NINCDS-ADRDA criteria (published in Neurology, 1984)</p> <p>Dementia with Lewy Bodies: International Consensus Criteria (ICC) for the diagnosis of DLB (report of the consortium on DLB international workshop, published in Neurology, 1996)</p> <p>Vascular Dementia: National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)</p>
Image analysis method	Blinded image evaluation by 3 independent nuclear medicine physicians at image review center in Oslo, Norway
Image acquisition method	<p>All cameras were capable of SPECT imaging.</p> <p>Reconstruction methods were not defined in the protocol and may have varied by study site.</p>
Prespecified efficacy thresholds	Sensitivity greater than 65% and specificity greater than 73%
Disease severity of patients at baseline	Not enough information to assess
Disease severity of patients completing 12 month follow-up assessment (PPP) (N=235)	<p>Not enough information to assess in detail.</p> <p>At 12 month f/u, clinical diagnoses were:</p>

	DLB Probable DLB – 86 (37%) Possible DLB – 25 (11%) AD Probable AD – 84 (36%) Possible AD – 29 (12%) VD Probable VaD – 1 (<1%) Possible VaD – 9 (4%)
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Study PDT301 was originally designed to determine the sensitivity and specificity of the visual assessment of Datscan SPECT images in differentiating between “probable DLB” and “non-DLB” subjects as determined by the clinical diagnosis (SOT), established by an independent consensus panel (CP) at baseline and after the 12-month follow-up. The clinical diagnosis was established by published consensus criteria (1996 criteria) for DLB diagnosis, and was based on all clinical and neuropsychiatric data collected during the study period, without knowledge of Datscan imaging results.

The revised objective for the U.S. study report was stated as:
 “To determine, in subjects with symptoms and signs of dementia, the sensitivity and specificity of the visual assessment of Datscan SPECT images in detecting or excluding a SDD. The presence of a SDD was indicated by a SOT diagnosis of DLB, and the absence of a SDD was indicated by a SOT diagnosis of another form of dementia (AD or VaD) that is not associated with a SDD.”

The clinical diagnoses (SOT) were designated as probable DLB, possible DLB and non-DLB. These diagnoses were then compared to the blinded image evaluations to determine sensitivity and specificity for detecting or excluding SDD. Measurements of sensitivity and specificity were performed with the “probable DLB” compared to non-DLB, as well as including the “possible DLB” group in the efficacy analysis.

Reviewer’s Comments:

PDT301 was designed to determine the diagnostic performance (sens/spec) of DaTSCAN in differentiating between “Probable” DLB subjects and non-DLB dementia subjects. Clinical diagnoses were categorized as probable DLB, possible DLB, or non-DLB by the off-site consensus panel (3 DLB experts) based on the 1996 published consensus criteria for DLB diagnosis. The CP had knowledge of the on-site investigator’s baseline clinical diagnosis and reviewed all available clinical data, including prior imaging examinations (excluding DaTSCAN results). Multiple statistical analyses were then performed using the blinded image reads compared to different combinations of these clinical diagnosis (SOT) categories. This method of determining sensitivity and specificity using “probable” DLB and excluding “possible” DLB has the

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potential to confound efficacy measurements. For the primary efficacy analysis, “probable” DLB and non-DLB will be compared to the blinded image reads.

It should also be noted that dopamine agonists and antagonists were allowed as concomitant medications in the trial. The applicant has not submitted human data to support the claim that dopamine agonists and antagonists do not alter the DaT protein distribution in the striatum or Datscan image results.

Of greater importance, baseline clinical diagnosis is not an acceptable SOT for DLB, as long follow-up is needed to make this clinical diagnosis. Even with longer follow-up, a definitive diagnosis of DLB cannot be made (see FDA neurology consult in DARRTS by Dr. Gerald D. Podskalny, page 5 of 17). It is unusual that the sponsor would utilize 36 month follow-up to establish clinical diagnosis for the study in early Parkinsonian subjects (304), but only baseline clinical diagnosis for DLB subjects.

Additionally, the clinical diagnosis was determined using the 1996 consensus criteria for the diagnosis of DLB. The 1996 consensus criteria are thought to have suboptimal sensitivity for making the DLB diagnosis. New consensus criteria (clinical and pathologic) for DLB diagnosis were published in 2005 and are thought to improve the diagnostic accuracy of the clinical diagnosis and pathological confirmation of DLB. (Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium, Neurology, 65:1863-1872). Therefore, the use of clinical diagnosis as a SOT undermines the reliability of efficacy results for study 301. In this reviewer’s opinion, study 301 does not qualify as a confirmatory study to support the use of DaTSCAN in subjects with dementia.

Table 6: Study 304

Study 304	
Design	Phase 3, multi-center (10 centers), open-label, non-randomized study to determine the predictive value of Datscan SPECT in differentiating between subjects with early features of Parkinsonism, other causes of tremor (ET) and healthy volunteers
Protocol date (Original)	11/16/1998
Amendments to protocol	12/21/1998 07/01/1999, 10/04/1999, 08/14/2000, 04/12/2001, 06/27/2001, 12/07/2001, 07/26/2002, 04/28/2004, 08/05/2005

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Statistical plan date	Not stated
Study dates	1/18/1999 to 6/28/2005
Inclusion criteria	<p>Subjects with early features of Parkinsonism:</p> <ol style="list-style-type: none"> 1. Male or female 30 to 90 years of age 2. Cardinal features of Parkinsonism 3. Unified Parkinsons Disease Scale (UPDRS) part III scoring ≤ 16 <p>Healthy volunteers:</p> <ol style="list-style-type: none"> 1. Male or female 30 to 90 2. Good age-appropriate health as established by clinical examination
Exclusion criteria	<ol style="list-style-type: none"> 1. History of stroke or cerebral vascular 2. Disease 3. Psychiatric illness other than depression 4. Positive for dementia by DSM IV-R 5. History of repeated head injury 6. History of definite encephalitis 7. Neuroleptic treatment at onset of symptoms or MPTP exposure 8. Features suggestive of MSA or PSP 9. History of response to drug therapy suggested idiopathic PD, > 5 year history
Primary endpoints	Sensitivity and specificity of DaTSCAN images (BIE) in differentiating between "Probable" or "Possible" PD versus non-PD (using the SOT assessment at 36 months).
Secondary endpoints	<ol style="list-style-type: none"> 1. Institutional visual read of Datscan images at T=0 compared to clinical diagnosis by blinded, institutional neurologist at T=3 months. 2. Sens/spec, accuracy, PPV, NPV for the institutional read and the BIE reads at T=0 compared to the clinical diagnosis established by 2 independent MDS at T=18 and T=36 months. 3. Sens/spec, accuracy, PPV and NPV for the institutional, clinical diagnosis at T=0

	<p>compared to the 2 independent, MDS diagnoses at T=18. Same analyses also performed for the institutional clinical diagnosis at T=0 compared to the consensus diagnosis by the 2 independent MDS at T=36.</p> <p>4. Exploratory analyses of the groups of probable PD, possible PD, and non-PD as determined in the IIE video assessment.</p> <p>5. The confidence levels of the clinical diagnosis of idiopathic Parkinson’s Disease.</p> <p>6. Sens/spec, accuracy, NPV, and PPV for the independent SPECT readers at T=0 compared to on-site clinical diagnosis at T=18 and T=36.</p> <p>7. Analysis of the stability of Datscan SPECT findings (institutional visual read and independent SPECT read) over time: sens/spec, accuracy, PPV, NPV for both the institutional read and the independent BIE reads at T=18 and T=36 compared to the consensus diagnosis by 2 independent MDS at T=36 months.</p> <p>8. Inter-reader agreement between Datscan SPECT readers and inter-reader agreement between independent video readers.</p>
Safety endpoints	Only AEs were analyzed for the U.S. CSR
Standard of truth	Consensus diagnosis by 2 movement disorder specialists by review of taped video assessment performed at T=36 months
Diagnostic criteria utilized for consensus diagnosis	<p>Parkinson’s Disease</p> <p>1. Brain Bank Criteria</p> <p>(“Probable” and “Possible” Parkinson’s Disease were grouped together and both considered PD; ET and “other” were considered as non-PD)</p>
Image analysis method	BIE by 3 independent readers at (b) (4)

	<p>(b) (4) (background not given, but readers were trained by sponsor in Datscan interpretation)</p> <p>(1 institutional read also performed)</p>
Image acquisition method	<p>All cameras were capable of SPECT imaging.</p> <p>Reconstruction methods were not defined in the protocol and may have varied by study site.</p>
Primary statistical hypotheses	None stated
Disease severity of patients at 36 month follow-up SOT assessment (N=102)	<p>Not enough information to assess in detail.</p> <p><u>UPDRS scores (means):</u></p> <p>“Probable” PD group - 20.3 Non-PD group - 7.1</p> <p><u>Diagnoses:</u></p> <p>Parkinson’s Disease Probable PD - 66 (65%) Possible PD - 5 (5%)</p> <p>Non PD – 31 (30%)</p>
Disease severity of patients at baseline pre-dose clinical assessment (N=102)	<p>Not enough information to assess in detail.</p> <p><u>UPDRS scores (means):</u></p> <p>“Probable” PD group - 10.8 Non-PD group - 6.4</p> <p><u>Diagnoses:</u></p> <p>Parkinson’s Disease Probable PD - 44 (43%) Possible PD - 37 (36%)</p> <p>Non PD – 21 (21%)</p>

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Study PDT304 was originally designed to determine the predictive value of Datscan SPECT imaging in differentiating between subjects with early features of Parkinsonism, other causes of tremor (mainly ET), and healthy volunteers. The clinical diagnosis (SOT) was determined by review of taped video assessment (performed at T=18 months and T=36 months) by 2 movement disorder specialists. The primary endpoints

in the European study report were sensitivity, specificity, accuracy, PPV and NPV for both the 1) onsite DaTSCAN image read, and 2) the BIE of DaTSCAN images by 3 independent readers at the (b) (4), as compared to the SOT at T=36 months.

The revised primary endpoints for the U.S. study report were stated as:

“In the reanalysis for the U.S. CSR, sensitivity and specificity for the detection or exclusion of a SDD will be the focus of discussion. The clinical diagnosis established at 36 months was used as the SOT (surrogate for SDD detection). Subject groups were defined as: 1) “Probable” PD, 2) “Possible” PD, 3) Non-PD (ET), and 4) Other. Sensitivity and specificity for the visual image assessments for detecting or excluding a SDD were determined for the following comparisons: 1) “Possible” or “probable” PD vs. non-PD (Primary efficacy analysis), 2) “Probable” PD (SDD present) vs. non-PD (absence of SDD), and 3) “Probable” PD vs. “Possible” PD or non-PD.” The applicant then states in the U.S. study report that these comparisons were done for the on-site clinical diagnosis and separately for the T=36 SOT evaluation, using both the BIE results and the on-site DaTSCAN read.

Reviewer’s Comments:

Study PDT304 is acceptable with regards to study design and the population of subjects (early PS) likely reflects the population of patients to benefit most from Datscan imaging. The drop-outs which occurred over the course of the 36 months follow-up period did not significantly change the patient demographics when comparison is made between the 36 month follow-up (efficacy) population and the baseline population of subjects.

For the primary efficacy analysis, the sponsor evaluated “probable” or “possible” PD versus non-PD to determine the diagnostic performance. There was a pre-specified statistical analysis plan, pre-specified endpoints, and the SOT and image analysis protocols are acceptable. However, there were no pre-defined statistical success thresholds for this study, which is the preferred method for conducting a confirmatory clinical trial.

It should be noted that dopamine agonists and antagonists were again allowed as concomitant medications in the trial. As stated in the comments for study PDT301 the applicant has not submitted human data to support the claim that dopamine agonists and antagonists do not alter Datscan image results.

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Table 7: Study 003

Study 003	
Design	Phase 3, multi-center (6 centers), open-label, non-randomized study to determine the sensitivity and specificity of striatal uptake of Datscan in patients with a documented clinical diagnosis of PD, MSA, PSP or definite ET
Protocol date	11/27/1997
Amendments	07/09/1997, 07/15/1997, 09/17/1997, & 11/27/1997
Statistical plan date	Not stated
Study dates	8/25/1997 to 2/24/1998
Inclusion criteria	<p>Patients:</p> <ol style="list-style-type: none"> 1. PD, MSA or PSP and satisfaction of the UK Parkinson's Disease Society Brain Bank criteria step 1, or 2. ET and satisfaction of the Findley & Koller definite ET definitions <p>Healthy Volunteers: Male and females 50 to 80 years</p>
Exclusion criteria	<p>General:</p> <ol style="list-style-type: none"> 1. Use of prohibited medications (including anti-Parkinson's disease therapy) 2. > 15 mSV/year occupational exposure to radiation 3. History of substance abuse 4. Abnormal lab values deemed clinically relevant by investigator 5. Females of child bearing potential not on birth control 6. Pregnant/lactating females <p>PD patients:</p> <ol style="list-style-type: none"> 1. Evidence of CVD, brain tumor or

	<p>communicating hydrocephalus 2. Positive DSMv IVR assessment for dementia 3. History of repeated stroke or head injury 4. History of definite encephalitis</p> <p>Please see protocol for additional PD, MSA, PSP and ET specific exclusion criteria (pages 31-32)</p>
Primary endpoints	Sensitivity and specificity in differentiating between PS (SDD) and non-PS (ET, no-SDD) based on institutional read of DaTSCAN compared with clinical diagnosis
Secondary endpoints	<p>1. Blinded, consensus read of DaTSCAN images compared to clinical diagnosis, only subjects with “consensus” read were included.</p> <p>2. Analysis of quantitative assessments of region of interest data.</p>
Safety endpoints	AEs, labs, EKG, vital signs
Standard of truth	Pre-existing, documented clinical diagnosis confirmed at baseline by on-site study investigators
Diagnostic criteria utilized for baseline clinical diagnosis	<p>PD:</p> <p>1. Documented diagnosis of PD and satisfaction of UKPDS Brain Bank criteria step 3 2. Documented evidence of positive challenge test to dopamine</p> <p>MSA:</p> <p>1. Documented diagnosis of MSA 2. Satisfaction of the Consensus Committee of the American Autonomic Society and the American Academy of Neurology diagnosis criteria (Neurology 1996;46:1470)</p>

	PSP: 1. Documented diagnosis of PSP 2. Satisfaction of the NINDS-SPSP clinical criteria for diagnosis (Neurology 1996;47:1-9) ET: 1. Documented diagnosis of ET 2. Satisfaction of Findley & Koller definite essential tremor definitions and behavioral classifications for clinical diagnosis (Findley & Koller 1994)
Image analysis method	On-site image analysis by study investigators (Consensus blinded read also performed by 5 of the 13 study investigators, including 1 neurologist & 4 nuclear medicine physicians. Agreement between 3 of 5 readers was considered the “consensus” for that subject.)
Image acquisition method	All cameras were capable of SPECT imaging. Reconstruction methods were not defined in the protocol and may have varied by study site.
Number of subjects: Received study drug Evaluable for safety	224 224
Statistical hypotheses	None
Disease severity of patients	Not enough information to assess

Study DP008-003 was originally designed to determine the sensitivity and specificity of striatal uptake of DaTSCAN in patients with a documented clinical diagnosis of Parkinson’s disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) compared with essential tremor (ET) and healthy volunteers. The primary endpoint was stated in the European study report as “The primary efficacy variable was identified as the visual assessment of DaTSCAN striatal uptake as determined by the institutional read (clinical diagnosis of the patient by the study site).”

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The European study report also states “Secondary efficacy variables were identified as the visual assessment of DaTSCAN uptake as determined by the blinded read (consensus diagnosis of panel of reader, blinded to the clinical diagnosis, which was derived from the patient’s visual image alone).”

The revised primary endpoints for the U.S. study report were sensitivity and specificity of the on-site institutional read of Datscan SPECT images in differentiating between subjects with Parkinsonian Syndromes (PS), indicating presence of SDD, and non-PS (no SDD present) using the clinical diagnosis as the SOT.

Reviewer’s Comments:

Study DP008-003 was designed to assess the diagnostic performance of DaTSCAN in patients with an established clinical diagnosis of PD, MSA, PSP or ET. Disease severity and duration of symptoms for patients enrolled was not described in the study report. However, patients enrolled had a documented, clinical diagnosis of PD, MSA, PSP or ET. Therefore, it is reasonable to conclude the patients in this study were more advanced in their disease stage than patients in study PDT304, which also enrolled PD and ET patients.

There are additional review concerns for this study. These include lack of pre-specified statistical thresholds for success. Also, the documented, on site clinical diagnosis verified by study investigators is not an acceptable SOT, as it is subject to investigator bias. The on site image evaluation is also subject to bias. It is not clear if the on-site institutional readers were blinded, or had access to patient identity and/or clinical information during the institutional image evaluation. For the efficacy analysis, data comparing the blinded read to clinical diagnosis will be considered. The blinded “consensus” read was performed by 5 of the study investigators at the Amsterdam study site. A “consensus” was defined as agreement between 3 of 5 readers for a given subject’s images. “Mismatches” between DaTSCAN consensus image read results and clinical diagnoses were followed up with the individual study sites, but neither the baseline clinical diagnoses (SOT) nor the DaTSCAN consensus reads were changed following the mismatch analyses.

In contrast to studies PDT301 and PDT304, all anti-Parkinson’s disease therapy was withdrawn (time period decided on case by case basis) prior to subject initiation in this study.

This reviewer’s opinion regarding DP008-003 is that it is not acceptable as a confirmatory study, but provides supportive data for DaTSCAN use in patients with Parkinsonian disorders.

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Table 8: Walker Study

Walker Study	
Design	Investigator initiated, single center, proof of concept, open-label, non-randomized, cross-sectional and longitudinal study to investigate changes in the dopamine transporter using Datscan SPECT in subjects with DLB, other dementias and PD
Protocol date	Not stated
Amendments	None
Statistical plan date	Not stated
Study dates	6/1996 to 12/1999 (autopsy phase ongoing)
Inclusion criteria	Subjects meeting one of the following: 1. AD meeting the NINCDS/ADRDA criteria 2. PD meeting UK Parkinson's Disease Brain Bank criteria 3. DLB meeting the International Consensus Criteria for DLB (1996 criteria) 4. Healthy control subjects, age matched, not taking drugs known to affect the dopaminergic system
Exclusion criteria	Not stated
Primary endpoints (Longitudinal stage for U.S. study report)	Sensitivity and specificity of Datscan images compared to neuropathological diagnosis at autopsy
Secondary endpoints	Baseline clinical diagnosis compared to neuropathological diagnosis at autopsy (ROI-based semi-quantitative analysis of DaTSCAN striatal uptake ratios compared

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	to neuropathological diagnosis was also performed)
Safety endpoints	Spontaneously reported adverse events collected
Standard of truth	Blinded neuropathological diagnosis at autopsy
Baseline clinical diagnosis method	<p>Established by 1 clinician (on-site study investigator) at baseline based on fulfillment of the below criteria:</p> <p>Alzheimer's Disease: 1. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), published in Neurology, 1984.</p> <p>Dementia with Lewy Bodies: 1. Consensus DLB criteria (report of the consortium on DLB international workshop, published in Neurology, 1996)</p> <p>Parkinsons Disease: 1. UK Parkinson's Disease Society Brain Bank Criteria (Hughes et al 1992)</p>
Image analysis method	Blinded image evaluation based on consensus of 3 on-site readers (exception: 1 reader had access to patient identity & clinical information during the study, but did not review this information during image assessments)
Image acquisition method	A dedicated brain SPECT camera (Strichman Medical Equipment 810 linked to Macintosh computer) was used for all scans. Reconstruction method not defined.
Primary statistical hypotheses	None stated

Disease severity of patients at time of DaTSCAN imaging (baseline)	Not enough information to assess in detail. Average age of dementia onset: 73.6 years (range: 53 – 93) Average age at DaTSCAN imaging: 77.5 years (range: 58 – 95) Average time from onset of dementia to DaTSCAN imaging: approximately 4 years (Subjects with DLB had higher dementia scores than non-DLB subjects)
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The Walker study is an ongoing investigator-initiated study being conducted in the UK (12 investigators), and the only study to use neuropathological diagnosis at autopsy as the standard of truth. It was originally designed to investigate the pre and post-synaptic components of the striatal dopaminergic system (caudate/putamen radioactivity ratios) of patients diagnosed with DLB and to compare them with AD, PD patients and healthy controls. The applicant has utilized preliminary data from this study to determine the sensitivity and specificity of Datscan SPECT images in confirming the established clinical diagnosis of DLB patients.

Reviewer's Comments:

The Walker study is a small sample of patients which utilizes the optimal standard of truth of autopsy histopathology to confirm the clinical diagnosis. However, there were no measurements performed on the human brain slices to confirm binding of DaTSCAN to the DaT protein.

Although blinded image reads were performed by 2 of the 3 readers, one reader had access to clinical information throughout the study, including the clinical diagnoses, which introduces some potential bias into the image reads.

The Walker study also used the consensus DLB criteria published in 1996 to determine the neuropathological diagnosis at autopsy and baseline clinical diagnosis. As previously noted, DLB consensus criteria (clinical and pathology) have undergone changes since this time, and new criteria were published in 2005. Also of significant concern are the findings at autopsy of mixed pathology for a majority of subjects in this study. Patients with any findings of DLB at autopsy were classified as DLB, even if they had AD findings at autopsy and/or did not display a clinical picture of DLB. The new consensus criteria for DLB published in 2005 address this issue of mixed pathology for DLB and AD. Under the 1996 consensus criteria used for this study, it is estimated that

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“as many as 60% of AD cases may be considered to meet pathologic criteria for DLB using the 1996 criteria. Virtually none of these patients will have had the DLB syndrome...” (Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium, Neurology, 65:1863-1872).¹

It should also be noted that the longitudinal study phase (patients with autopsy data), the mean age for reported onset of dementia was 73.6 (median 73.5, range 53-93) and the mean age at time of Datscan was 77.5 (median 77.5, range 58-95). Therefore, on average, approximately 4 years passed from the reported onset of symptoms to when patients underwent DaTSCAN imaging. Thus, these patients were more advanced in their disease syndrome than patients initially presenting with dementia symptoms. This finding may undermine the value of efficacy results for this study, as Datscan imaging may be most beneficial in patients who have early signs/symptoms of dementia (or movement disorders), when the clinical diagnosis is difficult to ascertain.

These issues raise major questions regarding the reliability of efficacy measurements in the Walker study, and create significant doubt regarding the accuracy and reliability of data submitted for Datscan in patients with dementia (studies 301 and Walker).

Overall reviewer's comments:

Studies PDT301, PDT304, DP008-003 and the Walker study (longitudinal phase) were all designed to test the diagnostic performance of DaTSCAN SPECT imaging in differentiating between either PS and non-PS or DLB and non-DLB dementia subjects.

The phase 3 studies contain a heterogeneous mix of patient populations, with only partially defined disease severities for the included patients. There were no pre-specified thresholds for statistical success for studies PDT304, DP008-004 or the Walker study, which is the preferred method for conducting confirmatory studies. Furthermore, the SOT was determined based on different methods in each study, with only the Walker study using pathology as a SOT to confirm the clinical diagnosis. Using baseline clinical diagnosis of DLB (based on outdated consensus criteria) as a SOT, as performed in study 301, is not acceptable in this reviewer's opinion.

There are additional questions regarding blinding of the image readers and consistency of image interpretation methods across studies readers (imaging review charters not submitted). In study 003, on-site investigators participated in an unblinded image read. In the Walker study, one of the 3 image readers had access to patient identity and clinical information during the study. The above study design and conduct issues raise concern regarding the reliability of some efficacy measurements presented in the NDA.

There is also concern regarding the effect of dopaminergic medications on Datscan results. Only study 003 excluded subjects on these medications. Previous studies of related compounds (beta-CIT) have shown disagreement between clinical status and Datscan image results in patients receiving dopaminergic medications to treat

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Parkinson's disease at the time of Datscan SPECT imaging, which raises the concern for potential effects of these medications on Datscan performed characteristics.^{6,10}

With regards to the dementia studies, this reviewer's opinion is that no confirmatory studies exist in the NDA to support the reliability and accuracy of Datscan in differentiating between subjects with DLB and non-DLB dementia (AD). Furthermore, the clinical usefulness of Datscan in dementia subjects is doubtful when considering the mixed pathology seen in these patients at autopsy, as the scientific literature reveals most subjects with DLB will have beta amyloid plaque burden which meets AD criteria.⁴¹ Thus, the potential exists to misclassify patients with abnormal Datscan images as DLB, when AD is part of their clinical syndrome.

However, study 304 was adequately designed to measure the reliability and accuracy of Datscan in differentiating between PD and non-PD subjects who present with early signs of Parkinsonism. This study enrolled subjects who most likely reflect the population of patients for which Datscan imaging may be clinically useful. The SOT assessment and image read methods were also acceptable. In this reviewer's opinion, study 304 is an acceptable study to demonstrate the ability of Datscan to provide a reliable measurement of DaT protein distribution in the striatum in this population of patients.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The applicant's original proposed indication was:

Datscan is a radiopharmaceutical containing [¹²³I] ioflupane, indicated for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.

In review of the pre-clinical and clinical data submitted in this NDA, it was decided Datscan would best fit the indication category of "functional, physiological, or biochemical assessment", under the FDA Guidance for Industry, Developing Medical Imaging Drug and Biological Products, emphasizing the biochemical assessment sub-

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category. In the Advisory Committee briefing document, we proposed the alternate Datscan indication of:

“visualization of the dopamine transporter (DaT) distribution within the striatum by SPECT imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration”.

This indication more accurately reflects the nature of the submitted pre-clinical and clinical data submitted in the NDA, and was accepted by the sponsor as the revised, current proposed indication.

6.1.1 Methods

This efficacy review focuses on the original primary endpoints (sens/spec) and original statistical analysis plans of the phase 3 studies. These study data may be used as support for the clinical usefulness, reliability and accuracy (CFR 21, 315.5) of DaTSCAN for the revised, current indication stated above.

Reviewer’s Comments:

The applicant is not proposing to market DaTSCAN as a diagnostic test for any specific disease or condition. However, the submitted phase 3 efficacy studies were designed to evaluate the diagnostic performance (sens/spec) of DaTSCAN imaging in patients with symptoms or clinical diagnoses of Parkinsonism or dementia.

6.1.2 Demographics

Table 9 shows the baseline characteristics for the intent to diagnose population (ITD) for each study.

Table 9: Demographic Characteristics by Study – ITD.

Study	301 (N= 326)	304 (N= 179)	003 (N=224)	Walker (N=22, longitudinal phase)
Median Age Min, Max,	75 54, 90	63 33, 86	64 40, 80	78 58, 95
Male Female	57% 43%	57% 43%	61% 39%	59% 41%
Race Caucasian Black Asian	100% 0% 0%	98%	98% 1% 1%	Not given

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Reviewer's comments:

The patient populations enrolled in these studies are reflective of the proposed patient population with regards to age and gender. However, there is very little data on Datscan use in minority populations contained in the NDA.

6.1.3 Subject Disposition

Table 10 provides a summary of the subject disposition for each study included in the efficacy analysis.

Table 10: Summary of Patient Disposition by study.

Study	301	304	003	Walker (long. phase)
Enrolled	351	202	250	45
Dosed	326	179	224	45
SOT Evaluated	326	102	224	22
Image Evaluable	313	174	220	45
Efficacy	313	102	220	22
Primary Efficacy Evaluated	231	102	185	22

Table 11 shows the baseline characteristics and diagnoses for the dosed subjects and subjects included in the primary efficacy analysis (36 month follow up available) for study 304.

Table 11: Study 304 baseline characteristics and diagnoses between dosed and efficacy subjects.

	Dosed (Baseline) N=179 n (%)	Efficacy (36 follow-up) N=102 n (%)
Female n (%)	77 (43)	45 (44)
Age ≥ 65 n (%)	77 (43)	42 (41)
Age Median (Range)	63 (33 – 86)	61 (33 – 79)
Caucasian n (%)	176 (98)	102 (100)
Probable Parkinson's	79 (44)	44 (43)

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Possible Parkinson's	55 (31)	31 (30)
Benign Parkinson's Disease	8 (4)	6 (6)
Possible Essential Tremor	22 (12)	14 (14)
Other	15 (8)	7 (7)

Reviewer's Comments:

Study 304 disposition data reveals there were 179 subjects dosed and 174 subjects with evaluable images, but only 102 subjects with SOT evaluated and available for efficacy assessments. This is a largely a result of the 36 month follow-up period required to determine the clinical diagnosis (SOT) of PD or non-PD, and is not unexpected. An analysis of the dosed subjects and efficacy subjects (see table 11) reveals similarity in demographics between these subject groups.

Table 12 shows a summary of the causes for lack of completion within each study.

Table 12: Subject dispositions by Study – Enrolled Population.

	301 (N=351)	304 (N=202)	003 (N=250)	Walker (N=45)
Completed	323 (92%)	98 (49%)	223 (89%)	22
Early Termination	28 (8%)	103 (51%)	27 (11%)	18 (5 being followed)
Reason for Early Termination:				
Subject request/Withdrew consent	16 (5%)	46 (23%)	18 (7%)	10
MD/Sponsor/Investigator Request	2 (1%)	0 (0%)	2 (1%)	
Excluded from Participation	0 (0%)	10 (5%)	0	
Lost to follow-up	2 (1%)	32 (16%)	0	7
Adverse Event	1 (<1%)	0 (0%)	0	
Safety Reason (includes AEs)	0 (0%)	10 (5%)	0	
Protocol violation	3 (1%)	4 (2%)	7 (3%)	
Other	4 (1%)	1 (<1%)	0	1
Evaluated in SPECT BIE	322 (92%)	174 (86%)	223 (89%)	45 (100%)
Excluded from SPECT BIE (images unavailable)	7 (2%)	UNK	3 (1%)	
Evaluable for Efficacy	288 (82%)	102 (50%)	220 (88%)	22
Intent to Diagnose Population (ITD)	326 (93%)	102 (50%)	220 (88%)	45
Per-Protocol Population (PP)	288 (82%)	100 (50%)	157 (63%)	22

Table 13 provides a summary of protocol violations for each study.

Table 13: Major Protocol Violations by Study – Dosed Population.

	301 (N= 326)	304 (N=179)	003 (N=224)	Walker (N=45)
Main Study Violations				
Administered prohibited meds	0	0	0	Not available
Inclusion/Exclusion criteria	9 (3%)	2 (1%)	23 (10%)	
Study Procedures	0	4 (2%)	54 (25%)	
Follow-up Study Violations				Not available
Inclusion/Exclusion criteria	0	0	0	
Study procedures	0	0	4 (2%)	

Reviewer’s comments:

As seen in table 13, study 003 had the most protocol violations, with 66 subjects (44 PS, 13 ET, 9 HV) revealing 77 violations. These violations were related to inclusion/exclusion criteria (n=23 violations) and study procedures (54 violations). The violations related to study procedures were mainly due to subjects receiving > 5 mCi Datscan. These subjects were excluded from the PP population.

Table 14 shows the clinical diagnoses for subjects in each study as determined by the standard of truth assessments.

Table 14: Summary of Clinical Diagnoses (per SOT) by study.

Study	301 (N=242)	304 (N=102)	003 (N=220)	Walker (N=22)
Parkinsonian Syndrome (PS; SDD)	0	71 (70%)	158 (72%)	0
Possible PS	0	5 (5%)	158 (72%)	
Probable PS	0	66 (65%)		
Dementia with Lewy Bodies (DLB; SDD)	116 (36%)	0	0	14 (67%)
Possible DLB	27 (8%)	0	0	
Probable DLB	89 (27%)	0	0	
Non-PS/Non-DLB (No SDD)	126 (39%)	31 (30%)	62 (28%)	8 (33%)
ET	0 (0%)	14 (14%)	27 (12%)	
AD	125 (38%)	0	0	
Other	1 (<1%)	17 (17%)	35 (16%)	

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SDD Present	116 (48%)	71 (70%)	158 (72%)	14 (64%)
SDD Absent	126 (52%)	31 (30%)	62 (28%)	8 (36%)

6.1.4 Analysis of Primary Endpoint(s)

The original primary efficacy endpoints for studies PDT301, PDT304, DP008-003 were sensitivity and specificity of Datscan visual image interpretations compared to the clinical diagnosis as the SOT. Although initially not clearly defined, sensitivity and specificity compared to neuropathology at autopsy were the primary efficacy endpoints in the U.S. study report for the Walker study.

Each image assessment was classified as a true positive (TP), true negative (TN), false positive (FP), or false negative (FN). These data were then used to calculate the sensitivity and specificity.

Sensitivity was defined as: $\frac{nTP}{nTP + nFN}$

Specificity was defined as: $\frac{nTN}{nTN + nFP}$

Movement disorder studies (PDT304 and DP008-003)

For these tables, the primary efficacy was based on blinded image reads compared to the SOT assessment. For DP008-003, the blinded reads were not part of the primary efficacy analysis as defined in the study protocol.

As seen in table 15, the point estimate for sensitivity of Datscan images in differentiating between early Parkinsonism and other forms of tremor (non-Parkinsonism) was approximately 78%. The point estimate for specificity was 96% for all 3 readers.

Table 15: Study 304 sensitivity and specificity of Datscan in early Parkinsonism subjects.

	Sensitivity (95% CI)	Specificity (95% CI)
Reader A N=102	77.5 (66.0, 86.5)	96.8 (83.3, 99.9)
Reader B N=99	77.9 (66.2, 87.1)	96.8 (83.3, 99.9)
Reader C N=101	78.6 (67.1, 87.5)	96.8 (83.3, 99.9)

As seen in table 16, the point estimate for sensitivity of Datscan images in subjects with an established clinical diagnosis of PS (PD, PSP, DLB) versus non-PS (mainly ET) ranged from 92% to 97%. The point estimate for specificity ranged from 74% to 96%.

Table 16: Study 003 sensitivity and specificity of Datscan in subjects with documented clinical diagnosis of PD, PSP, MSA or ET.

	Sensitivity (95% CI)	Specificity (95% CI)
Reader A N=185	93.0 (87.9, 96.5)	96.3 (81.0, 99.9)
Reader B N=185	96.8 (92.8, 99.0)	74.1 (53.7, 88.9)
Reader C N=185	96.2 (91.9, 98.6)	85.2 (66.3, 95.8)
Reader D N=185	92.4 (87.1, 96.0)	92.6 (75.7, 99.1)
Reader E N=185	94.3 (89.5, 97.4)	92.6 (75.7, 99.1)

Reviewer’s comments:

Patients enrolled in study 003 had a documented, clinical diagnosis of PD, MSA, PSP or ET. Therefore, these patients were more advanced in their disease stage than the patients in study PDT304 (early PD and ET patients). This likely explains (at least partially) the higher sensitivity results obtained for study 003 compared to study 304. Over a period of years, true PD patients should reveal themselves and fulfill the clinical criteria for diagnosis. Furthermore, Datscan images should reveal abnormal signal in the striatum in patients who have been followed for years and fulfill the criteria for a PD diagnosis. The population of patients in study 003 likely does not reflect patients most likely to benefit from Datscan imaging, which are those with early Parkinsonism (such as study 304 patients). However, the observation that sensitivity of Datscan improves as patients progress from early Parkinsonism (study 340) to a documented diagnosis of either IPD, PSP, or MSA may strengthen the evidence in support of Datscan in patients with a Parkinsonian syndrome. In this reviewer’s opinion, study 304 and 003 results provide a reasonable representation of agreement between Datscan images and clinical status in patients suspected of having or clinically diagnosed with Parkinsonian syndromes.

In study 304, five of the seven (71%) subjects designated as “true false negatives” were receiving anti-Parkinson’s medication. The sponsor has not submitted data to support the claim that dopamine replacement therapy will not affect Datscan image findings. This issue is of significant concern and should be addressed in future clinical studies of Datscan.

Dementia studies (PDT301 and Walker)

For these tables, the primary efficacy was based on blinded image reads compared to the SOT assessment.

Table 17 shows the sensitivity point estimates of Datscan images in differentiating between “Probable” DLB and non-DLB dementia ranged from 75% to 80% for the 3 central, blinded readers. Specificity point estimates ranged from 89% to 91%. Of note, subjects classified as “Possible” DLB were not included in this analysis.

Table 17: Study 301 sensitivity and specificity of Datscan in subjects with clinical diagnosis of dementia.

	Sensitivity (95% CI)	Specificity (95% CI)
Reader A N=216	79.8 (69.2, 88.0)	91.2 (85.2, 95.4)
Reader B N=216	75.3 (64.2, 84.4)	88.5 (82.0, 93.3)
Reader C N=218	80.3 (69.9, 88.3)	90.5 (84.3, 94.9)

Table 18 shows the mean sensitivity point estimate (3 on-site readers) of DaTSCAN images in diagnosing DLB and AD (compared to pathology) was 78% and the specificity point estimate was 85%. The mean sensitivity of the baseline clinical diagnosis for DLB was 78% and the specificity was 46%.

Table 18: Walker study sensitivity and specificity for baseline clinical diagnosis and Datscan images compared to neuropathology.

	Sensitivity (95% CI)	Specificity (95% CI)
Baseline clinical diagnosis N=22	77.8 (40.0, 97.2)	46.2 (19.2, 74.9)
DaTSCAN N=22	77.8 (40.0, 97.2)	84.6 (54.6, 98.1)

Reviewer’s comments:

The numerical point estimates for sensitivity and specificity of Datscan in study 301 and the Walker study are similar, but the confidence intervals are notably wider in the Walker study, partially related to the small sample size (n=22). In the Walker study, the performance of the baseline clinical diagnosis was not optimal, and the specificity was notably lower than the specificity for Datscan imaging. The clinical and pathological diagnosis of DLB were based on 1996 consensus criteria (revised in 2005). As stated in the Walker study reviewer comments, under the old consensus criteria, it is postulated that up to 60% of AD patients could be wrongly categorized as DLB patients based on pathology findings, even if these patients never exhibited the DLB clinical syndrome. This issue and the use of only 1 on-site study clinician to determine the

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baseline diagnosis may account for the low performance of the Walker study baseline clinical diagnosis. This finding casts significant doubt on the accuracy of efficacy measurements in study 301 based on the SOT of baseline clinical diagnosis.

6.1.5 Analysis of Secondary Endpoints(s)

Movement disorder subjects (Study 304)

Table 19 provides results of a secondary efficacy analyses for study 304. Shown are the sensitivity and specificity point estimates of DaTSCAN central, blinded reads compared to the SOT clinical diagnosis performed at T= 18 months.

Table 19: Sens/spec of Datscan BIE reads compared to T= 18 months SOT.

Study 304	Sensitivity % (95% CI)	Specificity % (95% CI)
Video reader 1		
BIE Reader A N= 128	67.0 (56.9, 76.1)	75.0 (55.1, 89.3)
BIE Reader B N= 125	67.0 (56.7, 76.2)	75.0 (55.1, 89.3)
BIE Reader C N= 127	67.7 (57.5,76.7)	75.0 (55.1, 89.3)
Video Reader 2		
BIE Reader A N= 125	70.5 (60.3, 79.4)	83.3 (65.3, 94.4)
BIE Reader B N= 122	69.6 (59.1, 78.7)	80.0 (61.4, 92.3)
BIE Reader C N= 124	71.3 (61.0, 80.1)	83.3 (65.3, 94.4)

Reviewer's comments:

When compared to table 15 (T=36 month SOT), it is clear the diagnostic performance of Datscan improved when utilizing the T= 36 months SOT assessment compared to the T= 18 months SOT assessment. This is likely explained by a more accurate clinical diagnosis performed at 36 months of follow-up compared to 18 months.

Dementia subjects (Study 301)

Table 20 gives results of a secondary analysis for study PDT301 with the diagnostic differentiation of “probable” or “possible” DLB versus Non-DLB dementia.

Table 20: Study 301 sensitivity and specificity for “Probable” or “Possible” DLB vs. Non-DLB dementia.

	Sensitivity % (95% CI)	Specificity % (95% CI)
Reader A N=269	64.4 (55.6, 72.5)	91.2 (85.2, 95.4)
Reader B N=268	60.5 (51.5, 69.0)	88.5 (82.0, 93.3)
Reader C N=273	61.8 (53.1, 70.0)	90.5 (84.3, 94.9)

Reviewer’s comments:

When comparing the sensitivity results from table 20 to table 17, it is clear that sensitivity results are notably lower when the “possible DLB” group is included in the analysis for study 301. The lower sensitivity seen when “possible DLB” and “probable DLB” are combined in the analysis indicates that Datscan may not have adequate sensitivity in subjects with early signs of DLB, as the lower range of the confidence intervals in the above table approach 50% (flip of a coin). Conceptually, this may be explained (at least partially) by DLB patients having a loss of DaT protein that is not above the threshold (unknown) for Datscan detection. The scientific literature reports that DLB subjects have less dopaminergic depletion at presentation compared to Parkinsonian subjects, which may support the above reasoning and findings.

These results combined with the inadequate use of baseline clinical diagnosis of DLB (see reviewer’s comments in 5.3, under table 5) as a SOT raise significant doubt regarding the reliability of Datscan in measuring the DaT protein distribution in the striatum in dementia subjects. In this reviewer’s opinion, the sponsor has not provided sufficient evidence of Datscan effectiveness, (clinical usefulness, accuracy and reliability) as described in CFR 21, 315.5, for use in this patient population.

6.1.7 Subpopulations

No specific subpopulations were identified that resulted in differences in efficacy measurements.

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Overall reviewer comment regarding efficacy:

Following evaluation of the entire efficacy profile for the product, this reviewer concludes that study 304 was adequately designed and provides reasonable estimates of accuracy and reliability for Datscan imaging in subjects with early Parkinsonism. Study 003 also provides supportive evidence for Datscan clinical usefulness in subjects with Parkinsonism.

This reviewer's opinion is the NDA does not contain confirmatory data as described in the FDA radiopharmaceutical regulations (CFR 21, 315.5) to support the effectiveness of Datscan in measuring striatal DaT distribution in subjects with dementia.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Clinical information obtained after a single, intravenous injection of Datscan

Study CY 95.FP.I (single dose of Datscan, 3 mCi)

- 95% clearance of Datscan administered dose from the blood within 5 minutes post-injection, with 98% clearance after 15 minutes post injection.
- Blood activity remained stable beyond 5 hours post-injection, decreasing to approximately 1% of the injected dose within 48 hours post-Datscan injection.
- 60% of administered dose was eliminated in the urine at 48 post-Datscan injection.
- Brain radioactive uptake was approximately 7% of administered Datscan dose, with 30% of this concentrated in the striatum.
- Highest levels of radioactivity were measured in the lungs, liver and brain.
- Radiation dose estimates revealed an average effective dose equivalent of 0.024 mSv/MBq, or 2.66 mSv for a 3 mCi injection of Datscan.

Study CY 96.FP.II (single dose of Datscan, 3 mCi)

- Following SPECT imaging at multiple time points, ratios of specific (striatal) binding to non-specific binding were found to be stable between 3 and 6 hours post-Datscan administration.

Phase 3 development program

All sponsor initiated phase 3 studies utilized a Datscan dose of 3-5 mCi by intravenous injection. Most subjects received a single dose of Datscan, with a smaller number of subjects (study 304) receiving multiple doses of Datscan over long follow-up periods.

- Estimated radiation effective dose is calculated to be approximately 4 mSv for a 5 mCi single administration of Datscan.

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Reviewer's comments:

The above phase 1 and 2 studies provided the basis for the proposed single dose of 3-5 mCi of Datscan by intravenous administration. The sponsor did not conduct any dose ranging studies prior to initiating the phase 3 program. Pharmacokinetic parameters were not investigated in subgroups of patients with different baseline medical histories (renal/hepatic failure) or for different baseline demographic characteristics.

Phase 3 studies were conducted base on the above studies revealing SPECT imaging was feasible, allowing visual and semi-quantitative analyses of Datscan images, and with acceptable dosimetry results, following administration of a single 3 mCi Datscan dose. Clinical studies have been conducted with dose ranges of 3.3 to 7.8 mCi, but no evidence of increased efficacy in the upper dose ranges exists. Therefore, the dose limit of 5 mCi was somewhat arbitrarily chosen by the sponsor.

7 Review of Safety

Safety Summary

Safety data for Datscan from 8 clinical studies (n=942 subjects) and post-marketing data from 2000-2009 reveal no important safety signals for Datscan administration. There have been no deaths or serious adverse events attributable to DaTSCAN as determined by the study investigators. In addition, data from clinical laboratory evaluations, vital sign monitoring and ECG assessments have produced no important concerns regarding Datscan use.

7.1 Methods

The applicant has submitted safety data from nine studies, with a total of 942 subjects receiving at least one dose of Datscan.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The submitted studies for safety include one phase 1 study (CY95.FP.I), two phase 2 studies (CY96.FP.II & PDT02005), six phase 3 studies (PDT301, PDT304, DP008-003, PDT03007, PDT408 and Walker). For the Walker study, only spontaneously reported adverse events (AEs) were recorded and the data were not included in the pooled safety analysis.

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Table 21 shows a summary of subject diagnoses for each study included in the review of safety.

Table 21: Subjects in the safety analysis by study and diagnosis group.

Study	Parkinsonism (PD,PSP,MSA) N=409 (43%)	DLB N=168 (18%)	ET N=29 (3%)	HV N=57 (6%)	Other N=254 (27%)	Unknown N=25 (3%)	Total N=942 N, %
CY95.FP.I N %	0	0	0	12	0	0	12 (1)
CY96.FP.II	20	0	0	10	0	0	30 (3)
PDT02005	26	0	0	0	25	0	51 (5)
DP008- 003	160	0	29	35	0	0	224 (24)
PDT304	142	0	0	0	37	0	179 (19)
PDT301	0	168	0	0	158	0	326 (35)
PDT408	61	0	0	0	34	25	120 (13)

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Datscan safety data were pooled across the 8 clinical studies due to the small number of subjects enrolled in the studies and the similar design of the larger, phase 3 studies. Subjects in the phase 1 and 2 studies all received a single, 3 mCi dose of Datscan by intravenous injection. Subjects enrolled in study 304 received up to 3 doses of DaTSCAN over a 3 year period. Subjects in study PDT03007 previously participated in study 003 and received two doses of study drug (1 dose in each study). Fourteen subjects in study 408 received two doses of DaTSCAN. All other subjects received a single dose of DaTSCAN.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All patients (N=942) exposed were adults > 18 years of age who received a single administration of Datscan ranging from 3-5 mCi, which is consistent with the proposed dosage. As stated above (7.1.3), some subjects (studies 304 and 408) received up to three doses of Datscan separated by time intervals of approximately 12 months.

Table 22: Demographics of subjects in safety analysis by diagnosis.

	Parkinsonism (PD,PSP,MSA) N=409	DLB N=168	ET N=29	HV N=57	Other N=254	Unknown N=25	Total N=942
Age (yr)							
Mean	63	74	64	56	70	66	66
Min,max	35,86	54,90	46,80	32,79	25,89	31,81	25,90
Gender							
Male	61%	62%	69%	39%	55%	28%	57%
Female	39%	38%	31%	60%	45%	72%	42%
Missing	<1%			<1%			<1%
Race							
Cauc.	98%	100%	100%	93%	100%	96%	99%
Black	<1%			5%		4%	1%
Asian	1%						<1%
Other	<1%						<1%
Missing	<1%			2%			<1%

Reviewer's comments:

Demographics relating to age and gender reflect the target population. However, the safety studies were conducted in almost exclusively (99%) Caucasians. Therefore, there are little data evaluating the safety of Datscan in minority races.

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7.2.2 Explorations for Dose Response

Phase 1 and 2 studies were performed evaluating a single 3 mCi dose of Datscan administered intravenously with regards to biodistribution, clearance, and radiation dosimetry estimates. This dose was consistent with previously reported studies of ¹²³I-ioflupane performed in Finland.⁸ The final, proposed dose of 3-5 mCi was determined based upon adequate imaging results and acceptable radiation dosimetry estimates obtained in the phase 1 and 2 studies.

7.2.3 Special Animal and/or In Vitro Testing

Preclinical studies were performed to evaluate behavioral safety, cardiovascular and respiratory safety, potential Datscan interactions with therapeutic drugs for Parkinsonism, single and repeat dose toxicology, and genotoxicity of Datscan. No reproductive toxicity or carcinogenicity studies were performed, as the sponsor's request for a waiver of these studies was granted.

In conscious dogs monitored with telemetry, a study using up to 983X the maximum human dose (MHD) revealed no cardiovascular effects. There was also no treatment related effect on PQ duration, QRS interval and QTc duration at approximately 10000X the MHD, although increased blood pressure and heart rate were reported at this dose. In another dog study, Datscan (9828X MHD) induced an increased respiratory rate immediately after injection. However, no elevated respiratory rate was reported at lower doses.

In rats, behavioral changes such as hyperactivity and stereotypic behavior related to similarity in pharmacology between Datscan and cocaine were seen at very high doses, which were approximately 3000X or higher than the clinical dose of Datscan.

Datscan (0.65X – 648X MHD) was administered to male Sprague-Dawley rats and a modified Irwin-type Functional Observation Battery (FOB) conducted on the rats between 10 minutes to 8 days post dosing. There was no mortality. However, there was piloerection, labored respiration, increased defecation, touch reactivity, positional passivity, and alterations in muscle tone. The reported alteration in respiration was dose-related and treatment related, while significant alterations in muscle tone were observed at 648X MHD.

In rat models of Parkinsonism, the potential effects of Datscan on the pharmacological actions of L-DOPA, bromocriptine and amantadine were evaluated. The combination of Datscan 0.1 mg/kg and a DAT inhibitor, GBR-12935 (0.1 mg/kg), did not affect the stimulating activity of L-DOPA on locomotor activity in rats with substantia nigra bilaterally lesioned with 6-OHDA. However, combinations of Datscan (1mg/kg) and GBR-12935 (1mg/kg) did prolong the actions of L-DOPA. Furthermore, combinations of Datscan (0.1 and 1 mg/kg) and GBR-12935 (0.1 and 1 mg/kg) did not affect the

stimulating activity of bromocriptine and amantadine on locomotor activity. Thus, Datscan did not affect the locomotor activity when administered in this experimental model of Parkinsonism in combination with L-DOPA, bromocriptine and amantadine.

Single dose and repeat-dose toxicity studies were conducted in rats, rabbits and Cynomolgus monkeys. No treatment-related mortality was reported in any of these studies. Following a single dose injection to dogs, mydriasis, increased motility, and licking were reported during administration or immediately after administration of 29480X MHD FP-CIT to dogs and a NOAEL of 1 µg/kg (98.3X MHD) was obtained. Increased heart rate, blood pressure, respiratory rate, slight decrease in motility, mydriasis and restlessness were reported in Cynomolgus monkeys administered 5880X MHD and the NOAEL in the study was 0.3 µg/kg (17.7X MHD). During single dose toxicity study, a NOAEL of 10 µg/kg (294.8X MHD) was obtained in the rats. No change in body weight or clinical pathology was reported in rabbits following a single injection of 0.06 mg/kg (3604X MHD), the only dose employed in the study.

The 14-day repeat dose toxicity studies in rats revealed stereotype behavior, increased and violent physical activity, excessive sensitivity to external stimuli, and piloerection following a daily injection of 17688X MHD. However, no treatment-related clinical signs were reported in animals administered 0.006 mg/kg/day (176.88X MHD). There were scattered blood spots in the lungs of 1/5 female in the 8844X MHD group and histopathology of the lungs showed localized mild bleeding in males in the 294.8X MHD group and in males and females injected 8844X MHD. The NOAEL in this study was 10 µg/kg/day (294.8X MHD). There were stereotype and aggressive behavior in rabbits treated with 360X and 36000X MHD for 2-weeks while increased responses to external stimuli, protruding eyes with dilated pupils, and fast or labored respiration occurred in rabbits administered 90000X MHD. No serious clinical signs were reported in Beagle dogs administered up to 9828X MHD of Datscan. However, there was mydriasis, congestion of the visible mucosa, flushing of the pinnae, reddening of the skin, or panting at this dose. The NOAEL in this study was 1 µg/kg/day (98.3X MHD).

The standard ICH battery of tests, including two *in vitro* assays covering the endpoints of gene mutation (in bacteria) and chromosomal effects (in cultured human lymphocytes and in mouse bone marrow), were evaluated. The tests were negative, indicating that FP-CIT (Datscan) demonstrates no genotoxicity potential.

7.2.4 Routine Clinical Testing

The routine clinical testing of study subjects was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

[Please see Clinical Pharmacology section (4.4.2) for further details]

There have been no human studies to investigate Datscan drug interactions. Drug interactions with Datscan are considered possible based on the mechanism of action of reversible binding to the DaT protein. Drugs which bind the DaT protein could theoretically block or reverse Datscan binding to the DaT ligand. The applicant provides a list of drugs with potential to interfere with Datscan binding (4.4.2).

Datscan use in patients with impaired excretory or metabolic function has not been evaluated because of its single dose, microgram dosing regimen. The effects of age and gender differences on Datscan pharmacokinetics have not been evaluated by the applicant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pharmacological effects from Datscan are not observed in humans following the intravenous administration of the proposed dose of ≤ 0.325 micrograms. Estimates from phase 2 studies indicate that Datscan occupies less than 1% of DaT proteins in the brain, with no expected pharmacological effect at this level of occupancy. The sponsor estimates that approximately 6000 vials of Datscan would have to be administered to achieve a pharmacological effect.

7.3 Major Safety Results

Tabel 23 shows a summary of adverse events for all subjects in the safety analysis.

Table 23: Adverse event summary

	Overall n (%)	Possibly DaTSCAN related * n (%)
Number of adverse events	588	73
Subjects with at least one AE	231 (25)	39 (4)
Subjects with at least one AE leading to discontinuation from the study	10 (1)	0 (0)
Subjects with at least one serious AE	36 (4)	0 (0)
Subjects with at least one AE leading to death	5 (<1)	0 (0)

**Relation to Datscan administration was determined by study investigator*

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7.3.1 Deaths

Five subjects died during the conduct of the studies. Four of the subjects were enrolled in the PDT304 study and 1 subject was enrolled in the PDT301 study. The fatal events were bronchial carcinoma (466 days after dosing), pneumonia (899 days after dosing), femoral neck fracture, myocardial ischemia and left ventricular failure (225 days after dosing), sepsis (time after dosing not available), and femoral neck fracture (366 days after dosing). None of the fatal events were considered related to DaTSCAN administration.

7.3.2 Nonfatal Serious Adverse Events

A total of 36 (4%) subjects experienced at least one serious adverse event (SAE), and no subject experienced an SAE that was considered by the investigator to be at least possibly related to Datscan administration.

7.3.3 Dropouts and/or Discontinuations

A total of 10 (1%) subjects experienced an AE that led to discontinuation from the study, and no subject experienced a possible Datscan related AE that led to discontinuation from the study.

7.3.4 Significant Adverse Events

Overall, 588 AEs were reported, with 73 (12%) of these AEs considered by the investigator to be at least possibly related to Datscan administration. A total of 231 (25%) subjects experienced at least 1 AE, and 39 (4%) subjects experienced an AE that was considered by the investigator to be at least possibly related to Datscan administration. Of the 39 subjects who experienced an AE possibly related to Datscan, the most common was headache (n=13, 1%), nausea (n=8, <1%), and vertigo, dry mouth, hunger, and dizziness (3 each, < 1%).

Table 24 summarizes the most common AEs overall, by body organ system and severity. Overall, 110 (12%) subjects experienced a mild AE, 85 (9%) subjects experienced a moderate AE, and 32 (3%) subjects experienced a severe AE. The most common AEs were related to nervous system disorders (85 subjects, 9%), followed by musculoskeletal and connective tissue disorders and gastrointestinal disorders (51 subjects each, 5%), infections (50 subjects, 5%), general disorders and administration site conditions (41 subjects, 4%), and vascular disorders (29 subjects, 3%). For all other body organ systems, the percentage of subjects with AEs was \leq 2%.

Table 24: Most common adverse events by organ system and severity.

Adverse events by system organ class	Total N (%)	Mild N (%)	Moderate N (%)	Severe/ Incapacitating N (%)	Missing N (%)
Number of subjects with at least one AE	231 (25)	110 (12)	85 (9)	32 (3)	4 (<1)
Gastrointestinal	51 (5)	28 (3)	20 (2)	3 (<1)	0 (0)
General disorders & administration site AEs	41 (4)	24 (3)	14 (1)	2 (<1)	1 (<1)
Infections/Infestations	50 (5)	32 (3)	15 (2)	3 (<1)	0 (0)
Injury, poisoning & procedural complications	21 (2)	6 (<1)	8 (<1)	7 (<1)	0 (0)
Investigations	16 (2)	13 (1)	1 (<1)	0 (0)	2 (<1)
Musculoskeletal & connective tissue disorders	51 (5)	27 (3)	21 (2)	3 (<1)	0 (0)
Nervous system	85 (9)	47 (5)	31 (3)	6 (<1)	1 (<1)
Psychiatric	16 (2)	10 (1)	5 (<1)	1 (<1)	0 (0)
Respiratory, thoracic, mediastinal disorders	22 (2)	13 (1)	8 (<1)	1 (<1)	0 (0)
Vascular disorders	29 (3)	22 (2)	7 (<1)	0 (0)	0 (0)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 39 subjects who experienced an AE possibly related to Datscan, the most common was headache (n=13, 1%), nausea (n=8, <1%), and vertigo, dry mouth, hunger, and dizziness (3 each, < 1%).

7.4.2 Laboratory Findings

There were no clinically significant mean changes from baseline for any serum biochemistry or hematology laboratory test. Urinalysis assessments including baseline and post-injection urine pH and specific gravity revealed no clinically significant changes from baseline. Analysis of shifts from baseline to post-injection for serum biochemistry,

hematology and urinalysis laboratory tests revealed increases generally matched by decreases, suggesting the changes were not related to a drug effect.

7.4.3 Vital Signs

There were no clinically significant changes in mean values from baseline to post-injection for SBP, DBP or pulse rate. Analysis of shifts from baseline to post-injection for SBP, DBP and pulse rate revealed increases generally matched by decreases, suggesting the changes were not related to a drug effect.

7.4.4 Electrocardiograms (ECGs)

Of 794 subjects with pre and post-injection EKG assessments, 446 (59%) subjects had a normal ECG tracing pre and post-baseline, and 242 (30%) subjects had an abnormal ECG tracing pre and post-injection. Thirty-eight (5%) subjects had a normal ECG tracing pre-injection and an abnormal tracing post-injection, and 48 (6%) subjects had an abnormal ECG tracing pre- and a normal tracing post-injection.

EKG interval data were only obtained in studies 301 and PDT03007. Analyses were performed comparing the baseline values, post-injection values and change from baseline values for ventricular rate, PR, QRS, RR, QT, QTc, TQcF and QTcB intervals. No clinically significant changes in mean values were observed for any of these parameters, except for the QTc (mean change from baseline of 16.5), which was obtained in only 30 patients. As seen in table 25 (next page), the results for QTcF and QTcB did not reveal any clinically significant change in mean values. .

Table 25: Electrocardiogram descriptive statistics for QT intervals.

QT interval (msec)	N	318	318	318
	Mean (SD)	402.0 (33.14)	398.6 (37.05)	-3.4 (35.04)
	Min, Max	327, 497	316, 495	-124, 108
	Median	402.0	400.0	-7.0
QTc interval (msec)	N	30	30	30
	Mean (SD)	399.8 (32.68)	416.3 (39.29)	16.5 (48.85)
	Min, Max	340, 469	340, 500	-61, 103
	Median	400.0	415.5	22.5
QTcF interval (msec)	N	318	318	318
	Mean (SD)	414.8 (25.66)	413.2 (27.64)	-1.6 (28.83)
	Min, Max	348, 497	343, 507	-88, 99
	Median	414.0	411.5	-4.0
QTcB interval (msec)	N	318	318	318
	Mean (SD)	421.4 (28.82)	420.5 (30.85)	-0.9 (33.63)
	Min, Max	348, 503	315, 520	-130, 106
	Median	419.0	418.5	-5.0

Reviewer's comment:

The overall EKG assessment results do not raise a significant safety concern for Datscan

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

Not studies were performed secondary to Datscan given as a single 3-5 millicurie intravenous injection, containing less than 0.325 micrograms drug product.

7.5.2 Time Dependency for Adverse Findings

Time of onset, duration, action taken, and outcome of AEs were not analyzed in the ISS.

7.5.3 Drug-Demographic Interactions

The incidence of AEs was analyzed in the following subgroups:

- < 65 years of age and ≥65 years
- < 75 years of age and ≥75 years
- Males and females
- Race groups

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A greater percentage of subjects in the < 65 years of age group compared to the > 65 years group reported at least 1 AE, 28% vs. 22%, respectively. However, the severity and types of AEs reported in these groups are similar, and the overall differences do not appear to be clinically significant.

In the < 75 years of age group compared to the > 75 years group, a greater percentage of subjects reported at least 1 AE, 27% vs. 17%, respectively. The differences in severity and types of AEs reported in these groups do not appear to be clinically significant.

Overall, 23% of male subjects and 27% of female subjects experienced at least 1 adverse event. Again, the severity and types of AEs reported in males and females were similar and there were no clinically significant findings in this analysis.

7.5.4 Drug-Disease Interactions

An analysis of AEs by diagnosis group or any other disease-related factor was not performed.

7.5.5 Drug-Drug Interactions

No studies have been performed to investigate drug-drug interactions for Datscan.

Reviewer's comments:

Evaluation of medication effects on Datscan imaging results will be an important part of the post-marketing program. (b) (4)

Previous studies of related compounds (beta-CIT) have shown disagreement between clinical status and Datscan image results in patients receiving dopaminergic medications to treat Parkinson's disease at the time of Datscan SPECT imaging, which strengthens the concern regarding the potential effects of these medications on the performance characteristics of Datscan. ^{6,10}

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity study was conducted for Datscan. The sponsor requested a waiver for carcinogenicity studies and the waiver was granted.

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7.6.2 Human Reproduction and Pregnancy Data

There are no data on Datscan exposure in pregnant or lactating women including inadvertent exposure during the drug development program or in the post-marketing data. It is not known if Datscan is excreted in human milk. However, free iodine-123 is known to be excreted in human milk. Based on batch data provided by the sponsor, the level of free iodine-123 present in the final drug product is expected to be < 3%.

7.6.3 Pediatrics and Assessment of Effects on Growth

There are no data on Datscan use in pediatric subjects. The sponsor requested, and was granted a waiver for the assessment of safety and effectiveness of the product in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:

There have been no clinical reports of overdose in patients with Datscan.

Drug Abuse Potential, Withdrawal and Rebound:

Not applicable to Datscan, which is administered as a single intravenous injection.

The mass quantity in a single administration of Datscan is < 0.325 micrograms and does not produce pharmacological effects in humans. The sponsor estimates that approximately 6000 vials of Datscan would have to be administered to achieve a pharmacological effect, which would involve administering approximately 15 liters of the other components in a Datscan vial. The sponsor states that such quantities of the product would not be available at any single time

7.7 Additional Submissions / Safety Issues

A PSUR was submitted July 7, 2009, covering the period July 28, 2008 to June 17, 2009. There were no deaths or serious reactions following the administration of Datscan in Europe. There were no non-serious reactions requiring changes to the European Datscan label.

8 Postmarket Experience

Datscan is approved for marketing in 32 countries. Estimates of patient exposure are based on number of vials shipped by the manufacturing site. Up to 7/27/2008, it is estimated that over (b) (4) patients have been exposed to Datscan. There have been no deaths reported from Datscan administration.

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Up to 7/27/2007, a total of 5 cases of severe pain on injection (4 from the same hospital) were received. One report of a serious adverse event following Datscan administration was reported. The patient was a 76 year-old man who developed an epileptic seizure 3 ½ hours after Datscan administration. The consulting neurologist attributed the epileptic seizure to hyponatremia.

Three spontaneous case reports from healthcare professionals comprising 4 non-serious unlisted reactions (epistaxis, vasovagal syncope, hypersensitivity, and sense of oppression) and one non-serious listed reaction (headache) were received during reporting for the 8th periodic safety update report (7/27/2007-7/27/2008).

9 Appendices

9.1 Literature Reviews and References

1. I.G. McKeith *et al*, Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium. *Neurology*, 65:1863-1872, December 2005.
2. Zuzana Walker *et al*, Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 78:1176-1181, 2007.
3. A literature review was performed 5/29/2009 using the *Up To Date* database and the phrase "dementia with lewy bodies".
4. Andrew J. Hughes *et al*, The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service, *Brain*, 125:861-870 2002.
5. A literature review was performed 5/29/2009 using the *Up To Date* database and the phrase "Parkinson's disease".
6. An FDA neurology consult was obtained to aid in the NDA review. This consult was written by Dr. Gerald Podskalny and is available in DARRTS.
7. Gunther *et al*, [¹²⁵I]β-CIT-FE and [¹²⁵I]β-CIT-FP are superior to ¹²⁵I]β-CIT for dopamine transporter visualization: autoradiographic evaluation in the human brain. *Nuclear Medicine and Biology*, 24:629-634, 1997.
8. J.T. Kuikka *et al*, Comparison of iodine-123 labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane and 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane for imaging of the dopamine transporter in the living human brain. *European Journal of Nuclear Medicine*, 22, No. 4:356-360, April 1995.
9. Lundkvist *et al*, [O-Methyl-11C] β-CIT-FP, a potential radioligand for quantification of the dopamine transporter: Preparation, autoradiography, metabolite studies, and positron emission tomography examinations. *Nuclear Medicine Biology*, 22, No. 7:905-913, 1995.
10. Fahn *et al*, Levodopa and the progression of Parkinson's disease. *NEJM*, 351:2498-508, 2004.

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9.2 Labeling Recommendations

Please see printed label for agree-upon final version of the document.

9.3 Advisory Committee Meeting

Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

August 11, 2009

Questions to the Committee:

1. Do the preclinical and clinical data demonstrate that DaTSCAN allows visualization of the dopamine transporter distribution within the human brain striatum? (DISCUSSION ONLY)

Committee Discussion:

Yes. The committee agreed that the data supported the contention that DaTSCAN allows visualization of the dopamine transporter distribution within the human brain striatum. One panel member suggested that a simple quantitative method may be needed to more readily interpret the findings.

2. Three phase 3 clinical studies assessed DaTSCAN images in comparison to clinical diagnoses (clinically diagnosed dementia or movement disorders). (DISCUSSION ONLY)
 - a. Is clinical diagnosis, as formed in these studies, a satisfactory diagnostic standard ("standard of truth") for the detection of abnormal dopamine transporter distribution within the human brain striatum?

Committee Discussion:

The committee did not come to a consensus regarding this question. Some of the panel members stated that clinical diagnosis is not an acceptable surrogate for a biochemical endpoint; thus, post-mortem pathology of the brain should be the standard of truth. Some panel members stated that clinical diagnosis can be a satisfactory standard of truth for Parkinson's Disease although post-mortem data is still the gold standard. A few panel members felt that this question was irrelevant since the committee is in agreement that DaTSCAN does what it purports to do and that a positive scan indicates abnormality but does not specify the disease.

- b. Does the acceptability of this standard depend on whether the clinical population had dementia or movement disorders?

Committee Discussion:

The committee was in agreement that acceptability of clinical diagnosis as a "standard of truth" does depend on whether the clinical population had dementia or movement disorders since the clinical progression of these diseases differ. Several members noted that the

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2008 discussion of amyloid imaging involved concerns that importantly differed from the DaTSCAN concerns.

3. Do the available data indicate a favorable risk to benefit profile for use of DaTSCAN as a tool to assist clinicians in the evaluation of patients with symptoms or signs suggestive of dopaminergic neurodegeneration?
 - a. If you answered, "no," discuss the types of clinical data that would be necessary to change your opinion.
 - b. If you answered, "yes," discuss whether the favorable profile applies to all patients or only specific subsets (e.g., only dementia or only movement disorders).

YES: 11 NO: 2 ABSTAIN: 1

Committee Discussion:

One panel member voted "No" because of reservations of DaTSCAN's clinical use; another member voted "No" because of safety concerns. Thus, there was no discussion of the types of clinical data that would be necessary to change their minds. The panels who voted "Yes" agreed that the favorable profile applies to all patients.

4. Discuss any considerations you regard as important for labeling or for subsequent clinical studies you believe should be performed.

Committee Discussion:

The committee recommended the following:

- *Clinical studies for use of DaTSCAN as a screening tool*
- *Clinical studies for use of DaTSCAN for diagnosis of early disease or disease progression*
- *Training standards for interpreting the scans should be developed and included in the labeling*
- *Development of a quantitative assessment of the image to provide standardization/validation of interpretation*
- *Studies to evaluate possible medication interactions*

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22454

ORIG-1

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INC

DA TSCAN

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/s/

PHILLIP B DAVIS

11/10/2009

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CLINICAL REVIEW

Application Type NDA
Application Number(s) 022454
Priority or Standard P

Submit Date(s) March 6, 2009
Received Date(s) March 9, 2009
PDUFA Goal Date September 9, 2009
Division / Office September 8, 2009/September 2, 2009

Reviewer Name(s) Phillip Davis, MD
Review Completion Date August 21, 2009

Established Name Ioflupane I 123
(Proposed) Trade Name DaTSCAN
Therapeutic Class Diagnostic Radiopharmaceutical
Applicant GE Healthcare

Formulation(s) Sterile aqueous solution 2mCi123I /ml
in 2.5 ml vial for intravenous injection
Dosing Regimen Single dose 3-5 mCi IV
Indication(s) Detecting loss of functional nigrostriatal
dopaminergic neurons by single photon
emission computed tomography
Intended Population(s) Patients presenting with symptoms and
signs suggestive of dopaminergic
neurodegeneration

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends approval of the NDA for Datscan (ioflupane I 123) for the indication of visualization of the dopamine transporter (DaT) distribution within the striatum by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs of Parkinsonism. This recommendation is based on review of the pre-clinical data and clinical data supporting the claim that Datscan binds to the DaT protein in the striatum, combined with the review of the two phase 3 studies evaluating the effectiveness of Datscan in patients with Parkinsonism. This approval is also based upon review of the safety data submitted from the European clinical development program and the post-marketing data.

1.2 Risk Benefit Assessment

This radiopharmaceutical has an acceptable risk benefit assessment based on the following qualities:

- Single dose (3-5 millicuries, < 0.325 micrograms) by intravenous administration
- Limited indication (Parkinsonism subjects)
- Limited patient population (adult patients)
- > ^{(b) (4)} patients exposed in the European market since 2000 without reports of serious adverse events or deaths related to study drug.
- Datscan SPECT imaging provides additional information currently unavailable to clinicians outside of research settings in evaluating subjects with Parkinsonism.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

None are needed.

1.4 Recommendations for Post-market Requirements and Commitments

The applicant should design and perform the following:

- A phase 4 study designed to assess the effect of anti-parkinsonian medications (at least carbidopa/levodopa and dopamine agonists) on Datscan performance characteristics.

2 Introduction and Regulatory Background

2.1 Product Information

Datscan is a radiopharmaceutical containing Iodine-123 labeled Ioflupane (ioflupane I 123 or [¹²³I]FP-CIT), a radioisotope-labeled cocaine analog, which binds to the dopaminergic transporter (DaT) protein in the brain. Datscan is administered by intravenous route, and the original submitted indication was for *detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.*

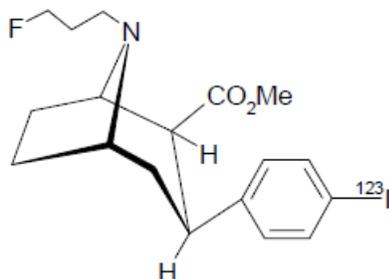
The revised indication, proposed by the Agency in the briefing document for the August 11, 2009 Peripheral and Central Nervous System Drugs Advisory Committee Meeting is *for visualization of the dopamine transporter (DaT) distribution within the striatum by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.* This indication was accepted by the sponsor and represents the current, proposed indication for Datscan.

(b) (4)

The Datscan final drug product contains ¹²³I-ioflupane, ioflupane, ethanol and sodium acetate (b) (4). The drug product is delivered as a sterile solution in 2.5 ml vials ready for intravenous injection.

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Structural Formula:



Molecular Formula: $C_{18}H_{23}F [^{123}I] NO_2$

Relative Molecular Mass: 427.29 (for the radioactive compound)

2.2 Tables of Currently Available Diagnostic Agents for Proposed Indication

Currently, there are no approved imaging agents in the U.S. for visualization of the dopamine transporter (DaT) distribution within the striatum.

2.3 Availability of Proposed Active Ingredient in the United States

This drug product is a new molecular entity and is not currently marketed in the U.S.

If approved, ^{123}I -ioflupane will be manufactured by GE Healthcare at the GE Arlington Heights facility in Illinois. The manufacturing of ^{123}I -ioflupane (b) (4)

materials used for the manufacturing of ^{123}I -ioflupane are controlled and released according to GE Healthcare specifications prior to use.

2.4 Important Safety Issues with Consideration to Related Drugs

Datscan contains the compound ioflupane, which is a cocaine analogue, labeled with the radioactive isotope, Iodine-123. Relevant safety issues include the presence or absence of pharmacologic activity following administration of the cocaine analog contained in DaTSCAN.

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As with all radiopharmaceuticals, radiation safety concerns are present secondary to the emission of gamma radiation (photon energy of 159 KeV) by the Iodine-123 radioisotope contained in Datscan. The reported effective dose of 3.94 milliseverts for a 5 mCi dose of Datscan represents an acceptable level of radiation exposure compared to guidelines for radiation workers, and is at the lower range of radiation effective dose for nuclear medicine imaging procedures.

It is not known whether Datscan is excreted into human milk. However, free Iodine-123 is secreted in human breast milk. Therefore, a decision regarding interrupting nursing following Datscan administration in order to minimized risks to nursing infants should be made by the patient's physician.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

DaTSCAN is approved in Europe and marketed in 32 countries. The sponsor relies solely on data from the European clinical development program, along with data from one ongoing investigator-initiated study in the United Kingdom as evidence of efficacy to support U.S approval. Pivotal phase 3 study issues regarding primary efficacy variable (sensitivity and specificity), statistical evaluation, and patient population were only discussed with the sponsor following completion of the European development plan.

In 2008, the agency held two face-to-face (Type C) sponsor meetings (1/31/2008 and 8/20/2008) regarding the sponsor's intention of seeking U.S approval of DaTSCAN. During the 8/20/2008 meeting, the sponsor stated an NDA for Datscan would be submitted based on existing data from the completed European development program. The Agency did not agree with this approach and listed a number of concerns regarding the studies performed for the European clinical development program. These concerns included lack of a validated standard of truth (SOT) for all the phase 3 studies performed by the sponsor, as well as a concern regarding the study reports selected to be submitted in the NDA as "principal studies to support US registration". The Agency commented that these principal studies may "not provide the primary basis for determining whether there is substantial evidence to support the claim of effectiveness of Datscan in detecting loss of functional nigrostriatal dopaminergic neurons, especially as it relates to its association with Parkinson's disease (PD)". Additionally, the Agency stated that the development program in the population of patients with Dementia with Lewy bodies (DLB) "appears to be somewhat more robust".

The Agency recommended a new phase 3 study "with a pre-specified clinically meaningful primary endpoint which would evaluate the diagnostic performance of your agent in the patient population of intended use, with the SOT consisting of a clinical diagnosis by a movement disorder specialist, and with Datscan images being evaluated by the properly conducted blind reads". The Agency also recommended to "involve a

representative number of US sites in such a study”. The sponsor did not conduct any additional phase 3 studies as recommended in this last meeting with the Agency.

2.6 Other Relevant Background Information

In the European market (32 countries), the approved indication for Datscan is more specific than the proposed U.S. indication. The primary European indication is for use in the diagnosis of subjects with clinically uncertain Parkinsonian syndromes (PS) to help differentiate them from subjects with essential tremor (ET), and for use in the diagnosis of subjects with clinically uncertain dementia with Lewy bodies (DLB) to help differentiate them from subjects with other types of dementia, such as Alzheimer’s Disease (AD). GE Healthcare has been manufacturing Datscan at the Eindhoven, The Netherlands facility since 2000 in compliance with European cGMPs. The European clinical development program data have been re-analyzed and re-reported for this NDA submission to support the proposed indication.

The dementia with Lewy bodies consortium published revised criteria for the clinical and pathologic diagnosis of DLB in 2005¹. As part of the criteria for the clinical diagnosis of DLB, the criteria include “Low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging” as a suggestive feature of DLB. The UK Brain Bank diagnostic criteria for the diagnosis of parkinsonian syndrome does not include imaging of the dopamine transporter as part of the supportive features for diagnosis.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The division consulted DSI regarding site inspections for this NDA. The pivotal studies utilized multiple study sites throughout Europe and the UK. Table 1 provides the study sites selected for inspection based upon these reasons:

- studies considered most important in demonstrating efficacy and safety claims (studies PDT-301 and PDT-304)
- (b) (4)
study sites (site #23, study PDT-301)
- number of patients enrolled at these site(s) exceeded the number of patients enrolled at all other study sites for the study of interest (site # 26, study PDT-301)
- imaging review centers for studies PDT-301 and PDT-304 were selected to investigate conformance with the blinded image evaluation protocol.

Table 1: Description of studies and study sites selected for DSI inspections

Site Name and Address	Report # / Protocol #	Number of subjects	Indication
Site # 23 Southampton Memory Assessment & Research Center	Study PDT-301 An open-label, phase 3, clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN, in subjects with dementia with lewy bodies.	18 enrolled/ 17 received study drug	<div style="background-color: #cccccc; height: 100px; width: 100%;"></div> (b) (4)
Site # 26 Neurologia 2, Spedali Civili di Brescia	Study PDT-301 An open-label, phase 3, clinical study to assess the striatal uptake of an intravenous solution containing the dopamine transporter radio-ligand, DaTSCAN, in subjects with dementia with lewy bodies.	29 enrolled/ 25 given study drug	Site # 26 enrolled more patients than any other center for study PDT301.
<div style="background-color: #cccccc; height: 40px; width: 100%;"></div> (b) (4)	Study PDT-301	235 evaluable for efficacy (PP)	Inspect (b) (4) for adherence to blinded image evaluation protocol.
<div style="background-color: #cccccc; height: 40px; width: 100%;"></div> (b) (4)	Study PDT-304	102 evaluable for efficacy (PP)	Inspect (b) (4) for adherence to blinded image evaluation protocol.

The DSI report revealed no major deficiencies that could compromise the integrity of the data.

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3.2 Compliance with Good Clinical Practices

In the application, GE Healthcare states the pivotal studies for safety and efficacy 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 Harmonization, and applicable national and local laws and regulations (e.g., Code of Federal Regulations Parts 50, 54, 56, 312, and 314). At each participating study site, the protocol and all amendments were approved by an Institutional Review Board. Written informed consent was obtained from each subject before any procedures or assessments were done and after the aims, methods, anticipated benefits, and potential hazards were explained. Subjects were informed that they were free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.” The applicant also states that “it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

3.3 Financial Disclosures

GE Healthcare pursued financial disclosure for all phase 3 studies submitted to support the efficacy of Datscan for the proposed indication, with the exception of study 003. This study was completed prior to 2/2/1999, making it exempt from financial disclosure requirements as stated in the March 20, 2001 FDA Guidance for Industry: Financial Disclosure by Clinical Investigators.

The applicant submitted a list of clinical investigators who participated in studies 301, 304 and the Walker study. Review of the financial disclosure documents reveals missing information for numerous investigators from study 301 (167 missing investigator disclosures), study 304 (26 missing investigator disclosures), and the Walker study (4 missing investigator disclosures). Reasons for inability to obtain financial disclosure from these investigators included “no longer at site”, “could not obtain”, “no response”, “left hospital”, “left the department”, and “not known at hospital”.

Additionally, five investigators who participated in sponsor-initiated phase 3-4 studies disclosed financial interests and/or arrangements with the sponsor. An investigator for study 301, site number (b) (4), received two grants (25,000 DM (b) (6) and 23,500 Euro on (b) (6)) to fund ongoing research. His site recruited 1% of the enrolled subjects for study 301. The applicant stated the investigator’s research grants did not influence study outcomes, and the results from this site were consistent with results seen at other study sites for overall study outcomes.

An investigator for studies 301 and 304, site numbers (b) (4), respectively, works as a consultant for GE Healthcare, for which he receives annual monetary compensation (15,000 to 28,000 pounds annually). GE states that consultancy fees paid to the investigator did not influence the outcomes of these studies for these reasons: 1) 4-5% of the enrolled subjects in studies 301 and 304 were recruited at the

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site of this investigator, and 2) Results from these sites were consistent with results at other study sites and for the overall study outcome for studies 301 and 304.

An investigator for study 301, site number (b) (4), reported receipt of a research grant on (b) (6) (23,500 Euro). The applicant states this grant did not influence study outcomes because: 1) This site recruited 1% of the enrolled subjects, and 2) Results from this site were consistent with results observed at other sites and for overall study outcomes.

Another investigator for study 301 at site number (b) (4) received two grants to fund ongoing research (25,000 DM received (b) (6) & 23,500 Euro received (b) (6)). The applicant states these grants did not influence study outcomes for these reasons: 1) This site recruited 1% of the enrolled subjects, and 2) The results from this site were consistent with results seen at other study centers and for the overall study outcomes.

The principal investigator for studies 301 and 304, site numbers (b) (4) respectively, reported receipt of research material (approximate value of \$25,000) provided by the sponsor. The sponsor states that this research material did not influence study outcomes for these reasons: 1) These sites recruited 1% and 17% of the enrolled subjects for studies 301 and 304, respectively. 2) The results from these sites were consistent with results observed at other study sites and for overall outcomes for studies 301 and 304.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review did not report issues that might affect efficacy or safety.

4.2 Clinical Microbiology

No issues to report.

4.3 Preclinical Pharmacology/Toxicology

The summary of the preclinical pharmacology/toxicology review states the sponsor provided adequate preclinical data on the safety of Datscan for the proposed indication, and the product was recommended for approval from the pharm/tox perspective.

The data showed high affinity and selectivity of Datscan for the Dat protein and this could provide in vivo images as a measure of the Dat protein distribution in the striatum. Datscan metabolites did not cross the blood brain barrier and no CNS pharmacological effect is expected following the metabolism of this compound. Due to similarity in the pharmacology of FP-CIT to that of other DaT ligands like cocaine, hyperactivity and stereotypic behavior was observed at high doses.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Datscan ($[^{123}\text{I}]\text{FP-CIT}$) is a radiolabeled cocaine analog which binds reversibly to the dopamine transporter protein (DaT) found in the axon terminals (located in striatum) of pre-synaptic nigrostriatal neurons. Nigrostriatal neuron cell bodies are located in the substantia nigra pars compacta region of the brain. These neurons have axons which project to and terminate in the striatum (putamen and caudate nucleus). Signals are transmitted from nigrostriatal neurons to striatal neurons by release of dopamine into the synapse, which binds to the post-synaptic striatal neurons. DaT proteins terminate neuronal signaling between nigrostriatal neurons and striatal neurons by participating in dopamine reuptake into the pre-synaptic nigrostriatal neurons, which prevents continuous neuronal firing.

Datscan is used as an indirect method to detect the loss of nigrostriatal neurons. The DaT protein is used as a marker for nigrostriatal neurons, and loss of these neurons will result in loss of the DaT protein. With nigrostriatal neuron loss, there should be less or no visualization of Datscan (by SPECT) in the striatum compared to individuals with any age-related changes.

4.4.2 Pharmacodynamics

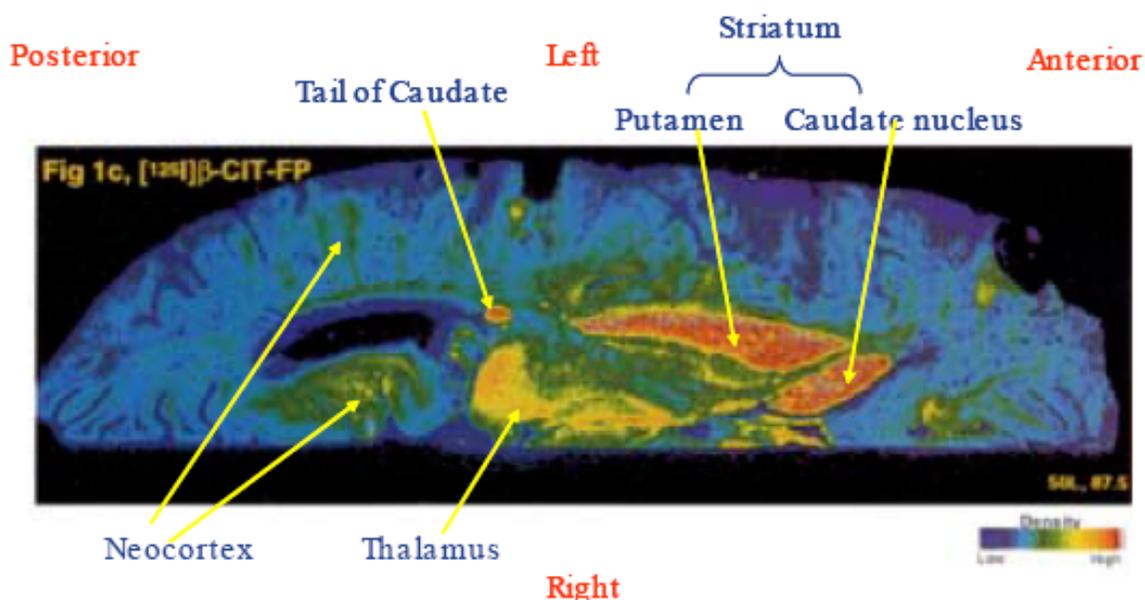
Pharmacological effects are not observed in humans following the intravenous administration of the proposed dose of ≤ 0.325 micrograms. Estimates from phase 2 studies indicate that Datscan occupies less than 1% of DaT proteins in the brain, with no expected pharmacological effect at this level of occupancy.

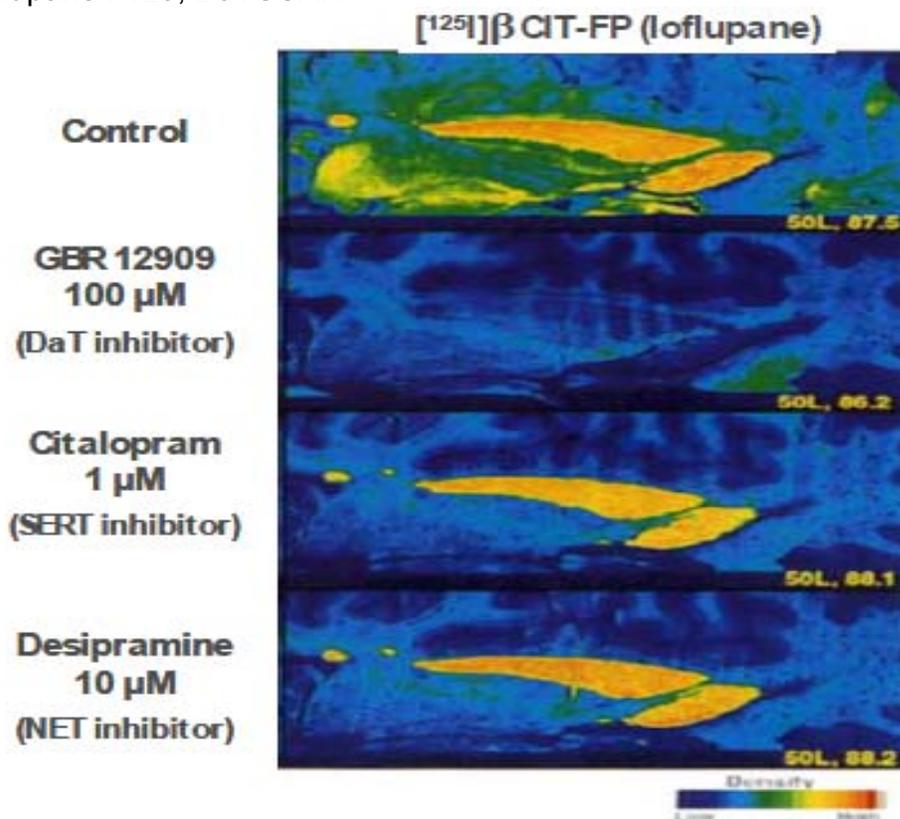
The affinity of FP-CIT for the human dopamine transporter (DaT) has been evaluated by the applicant in competitive binding studies at test agent doses between 0.1 nM and 100 μM . FP-CIT inhibited binding at the human recombinant dopamine transporter with a K_i of 0.62 nM and an IC_{50} of 0.70 nM. FP-CIT showed a 3- to 4-fold selectivity for the dopamine transporter over the serotonin transporter. Table 2 shows human recombinant targets where FP-CIT shows significant binding.

Table 2: Inhibition of Ligand Binding by FP-CIT (non radioactive)

Target	% inhibition (at conc.)	IC ₅₀	Ratio of target:DA transport IC ₅₀	K _i	Ratio of target:DA transport K _i
DaT	52 (1 nM)	701 pM	1	623 pM	1
Adrenergic NET	75 (1 μM)	229 nM	327	73 nM	117
SERT	79 (10 nM)	2.9 nM	4.14	1.9 nM	3.05

Literature reports of autoradiography of post-mortem human brain sections exposed to the radioligand have been performed in the presence and absence of competitive inhibitors in order to determine the selectivity and affinity of [¹²⁵I]-FP-CIT binding.





The above figures show autoradiograms obtained with [¹²⁵I]FP-CIT. To study the specificity of the binding of [¹²⁵I]-FP-CIT in post mortem human brain, competition studies with citalopram (SERT-specific ligand), desipramine (NET-specific ligand) and GBR 12909 (DaT-specific ligand) were carried out by Gunther *et al.* Citalopram reduced binding in the neocortex and thalamus with only minor effects in the striatum. This indicates that the binding in the cortex and thalamus is mainly to SERT. The NET inhibitor, desipramine, showed no effect on the level of striatal binding but reduced extrastriatal binding by 60 to 85%. Binding to all regions was abolished when including a high concentration of the predominantly DaT inhibitor, GBR 12909, leaving a low level of nonspecific binding. A concentration of 1 μM GBR 12909 reduced labeling in the caudate nucleus and putamen by approximately 50%. The data indicate selectivity of binding for the pre-synaptic DaT rather than post-synaptic dopamine receptors. The distribution of radioactivity within the brain sections is consistent with the selective affinity of the [¹²⁵I]-FP-CIT for the DaT.^{7,9}

Clinical Pharmacology Reviewer’s comments/conclusions:

The pharmacodynamic data show that Datscan has high affinity and some selectivity for DaT. The presence of different regional transporter densities supports the notion that a degree of contrast between DaT-rich and -deficient regions is achievable in normal individuals. Human physiology and pathology data show that DaT is located in dopaminergic neurons and that loss of these neurons is one characteristic of Parkinsonian disorders. These data support the use of Datscan as a qualitative marker of dopaminergic neuronal density.

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4.4.3 Pharmacokinetics

Phase 1 studies of Datscan revealed approximately 96% clearance from the blood at 15 minutes post injection, decreasing to 1% of the injected dose at 48 hours. Brain uptake was 7% of the injected Datscan dose, with 30% of brain uptake located in the striatum. The ratio of binding in the striatum to the occipital regions was approximately 3 to 1. Imaging of Datscan brain uptake is best performed between 3-6 hours post-administration, when binding levels are stable. Datscan is primarily excreted in the urine, with approximately 60% of injected dose voided by 48 hours.

In a phase 2 study, the highest absorbed radiation dose following Datscan administration was seen in the urinary bladder wall (0.054 mGy/MBq), followed by the lungs (0.043 mGy/MBq), lower large intestine (0.042 mGy/MBq) and the upper large intestine (0.038 mGy/MBq). Dosimetry estimates using OLINDA software indicate the total effective dose to be approximately 3.94 mSV for an administered activity of 5 mCi.

There have been no human studies to investigate Datscan drug interactions. Drug interactions with Datscan are considered possible based on the mechanism of action of reversible binding to the DaT protein. Drugs which bind the DaT protein could theoretically block or reverse Datscan binding to the DaT ligand. The applicant provides a list of drugs with potential to interfere with DaTSCAN binding, these include: benztropine (an anti-cholinergic tropane); cocaine (a tropane); mazindol, amphetamine, phentermine and methylphenidate (sympathomimetics); bupropion (an atypical anti-depressant used to treat nicotine addiction); and sertraline (and possibly other serotonin re-uptake inhibitors). Drugs with the ability to alter Datscan binding could possibly affect the diagnostic accuracy of Datscan SPECT imaging.

Reviewer's comments:

Assuming interference of Datscan binding occurs with certain medications, the most plausible consequence would be reduced or absent Datscan signal in the striatum. With reduced Datscan signal in the striatum, the most likely result would be increased false positive test results. Lack of clinical data on Datscan drug interactions presents a concern for use of Datscan imaging in patients taking the above mentioned medications, as well as for patients taking dopaminergic medications for Parkinsonism.

Previous studies of related compounds (beta-CIT) have shown disagreement between clinical status and Datscan image results in patients receiving dopaminergic medications to treat Parkinson's disease at the time of Datscan SPECT imaging.^{6,10} Future clinical studies will be needed to assess the effects of these medications on Datscan SPECT imaging results. At minimum, the sponsor may need to conduct a study designed to assess the effect of anti-parkinsonian medications (at least carbidopa/levodopa and dopamine agonists) on image results.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 3: Studies included for efficacy and safety evaluation

Study Number, Number of study centers, Location(s)	Study period, N, dosing	Design, Standard of truth (SOT), Image analysis method (IAM)	Primary endpoints
CY95.FP.I	N=12 healthy volunteers (HV) Single 3 mCi dose	Phase 1, single center, single group, open label, non-randomized, non-controlled PK and safety study of Datscan	Safety
CY96.FP.II	N=30 (10 HV, 20 PD patients) Single 3 mCi dose	Phase 2, single center, parallel group, open label, non-randomized, non-controlled study of Datscan uptake in various brain regions and assess safety and tolerability of Datscan	Safety
PDT02005	N=51 (26 PS patients, 25 non-PS patients) Single 3-5 mCi dose	Phase 2, non-comparative, open-label, non-randomized, non-controlled study of Datscan in differentiating between subjects with vascular Parkinsonism, cerebrovascular disease and HV	safety and activity
Phase 3 and 4			
Study 301 (PDT301) 40 centers in Europe participated	12/21/2003 to 6/28/2006 N=326 Single 3-5 mCi dose	Multi-center, open-label, non-randomized study SOT = expert clinical diagnosis at baseline as established by consensus panel of DLB experts IAM = BIE at image review center (b) (4)	Sensitivity and specificity of Datscan images in differentiating between DLB and non-DLB dementia.
Study 304 (PDT304) 10 centers in	1/18/1999 to 6/28/2005 N= 179	Multi-center, open-label, non-randomized study SOT = consensus	Sensitivity and specificity of Datscan images in

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Europe participated.	3 totals doses: 3-5 mCi at 3 separate time points (T=0, T=18, T=36)	diagnosis by 2 movement disorder specialists (MDS) by taped video assessment (T= 36 months), IAM = BIE by 3 independent readers at (b) (4)	differentiating between early Parkinsonism and other causes of tremor and healthy volunteers
Study 003 (DP008-003) 6 centers in Europe	8/25/1997 to 2/24/1998 N=224 Single 3 – 5 mCi dose	Multi-center, open-label, non-randomized study SOT = on-site clinical diagnosis at baseline by consensus criteria IAM = On site evaluation by study investigators (Central, BIE also performed for 2° efficacy analysis)	Sensitivity and specificity of DaTSCAN images in confirming the documented, clinical diagnosis of PD, MSA, PSP or ET
PDT03007 (All subjects previously participated in Study 003)	1/18/2000 to 10/27/2000 N=31 (8 HV, 20 PS patients, 3 ET patients) Single 3-5 mCi dose	Phase 3, multi-center, open label, non-randomized, non-controlled study to investigate change in Datscan uptake after 2 years	Semi-quantitative striatal uptake of Datscan
PDT408	N= 120 PS patients	Multi-center, open label, non-randomized, non-controlled study to assess the impact of Datscan imaging on patient diagnosis, physician confidence and management	Proportion of subjects in which clinical diagnosis of PS can be supported or excluded after Datscan imaging
Walker Study 12 investigators at one study site in the UK participated. (all image interpretations performed at (b) (4))	6/1996 to 12/1999, (autopsy phase ongoing) 22 subjects with available SOT assessment Single 3 mCi dose	Investigator-initiated, single-center, open-label, non-randomized, exploratory study SOT= neuro-pathological diagnosis at autopsy IAM = BIE performed according to 3 point qualitative scale by 3 readers in CP. A semi-quantitative analysis was performed by 1 blinded reader.	To determine: 1. Sensitivity and specificity of Datscan images in confirming diagnoses of DLB and AD. 2. Semi-quantitative analysis of Datscan uptake

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5.2 Review Strategy

Emphasis was concentrated on the review of Datscan pre-clinical and clinical pharmacology data in order to investigate the sponsor's claim that Datscan binds to the DaT protein with some specificity and selectivity. In addition, literature reports of autoradiography performed on human brain slices and in-vitro studies of ioflupane binding to human recombinant transporters (DaT, SERT, NET) allowed evaluation of the affinity and selectivity of Datscan for the human DaT protein^{7,9}. Of note, similar data was not presented in studies of human brain tissue from subjects with disease pathology analogous to subjects included in the proposed indication.

For the efficacy evaluation (demonstration of clinical usefulness, reliability and accuracy in a defined clinical setting), this review concentrates on the 4 studies described in table 3 and detailed in tables 5 through 8. The review will focus on the original primary endpoints of sensitivity and specificity of Datscan in differentiating between PS and non-PS movement disorders and between DLB and non-DLB dementia.

For the review of safety, information was evaluated from one phase 1 study (CY95.FP.I), two phase 2 studies (CY96.FP.II & PDT02005), six phase 3 studies (PDT301, PDT304, DP008-003, PDT03007, PDT408 and Walker). The total number of patients included in the safety analysis was 924 subjects.

5.3 Discussion of Individual Efficacy Studies/Clinical Trials

Overview

The applicant relies solely on data from the European clinical development program (studies PDT301, PDT304 and DP008-003), along with data from one ongoing investigator-initiated study (Walker study) in the United Kingdom to support efficacy claims. Prior to initiation of these studies, there were no agreements with the Agency regarding study designs and methods for pursuing U.S. registration. There were modifications of study objectives and statistical analyses to generate the U.S. clinical study reports from the European clinical study reports. The applicant performed post hoc analyses of each of these studies evaluating diagnostic performance of Datscan in the creation of the U.S. study reports.

All applicant sponsored phase 3 studies were multicenter, open-label, non-randomized clinical studies, originally designed to assess the diagnostic performance and safety of Datscan in subjects with dementia and/or movement disorders. The primary objectives of these studies as presented in the revised U.S. study reports were to determine the sensitivity and specificity of visual interpretations of Datscan SPECT images in detecting or excluding a striatal dopaminergic deficit (SDD). Visual assessments of Datscan images were compared to the clinical diagnosis (SOT) to determine sensitivity and specificity. With exception of the Walker study, the sponsor has utilized the clinical

diagnosis (SOT) as a surrogate for pathology in order to detect loss of functional nigrostriatal dopaminergic neurons, also known as a SDD. The sponsor does this by assuming presence of a SDD in subjects diagnosed with any of the Parkinsonian syndromes (IPD, PSP, MSA) and DLB, and assuming absence of a SDD in subjects clinically diagnosed with ET, AD and healthy volunteers.

Detailed imaging review charters were not provided for the phase 3 studies, but image acquisition and interpretation methods were briefly described in the study reports. Only one study, PDT301, had pre-defined statistical thresholds for success. Studies PDT304 and DP008-003 had pre-defined statistical analysis plans, but no pre-defined statistical thresholds. Of note, the clinical diagnoses were determined using different methods and by physicians with different areas of specialty for each study. Additionally, different blinding methods for image readers were used for each study.

Table 4 illustrates the basic revisions performed by the applicant to create U.S clinical study reports from the original European clinical study reports for studies considered pivotal in supporting efficacy and safety claims. For the remainder of this review, Study PDT-301 will be referred to as 301, Study PDT-304 will be referred to as 304, and Study DP008-003 will be referred to as 003.

Table 4: Comparison of European and U.S. study reports.

Study	301	304	003	Walker
Population	Dementia subjects (possible DLB, AD, VaD)	Early Parkinsonism subjects (PD and ET) and healthy volunteers	Subjects with documented clinical diagnosis of PD, MSA, PSP or ET and healthy volunteers	Subjects with clinical diagnosis of DLB, AD, or PD, and healthy volunteers
Pre-specified primary endpoints	Sensitivity (Sens) and specificity (Spec) in differentiating between “probable”-DLB and non-DLB	PPV, NPV, Sens, Spec, & Accuracy of DaTSCAN image assessments	Sens and Spec of DaTSCAN striatal uptake	Sens and Spec for visual image assessment and clinical diagnosis, SensQuantitative DaTSCAN uptake ratios
Primary endpoints for U.S. study report	Sensitivity and specificity for detecting or excluding a SDD	Sensitivity and specificity for detecting or excluding a SDD	Sensitivity and specificity of DaTSCAN images in differentiating between PS and non-PS subjects	Sensitivity and specificity of DaTSCAN images in confirming diagnoses of DLB, AD, PD and in healthy controls

Individual Studies

Table 5: Study 301

Study 301	
Design	Phase 3, multi-center (40 centers), open-label, non-randomized single dose study to determine the sensitivity and specificity of Datscan imaging in differentiating between subjects with Dementia with lewy bodies (DLB) and other forms of dementia (AD, VaD)
Protocol date (Original)	6/17/2003
Amendments to protocol	10/02/2003, 04/08/2004, 01/11/2005, 04/21/2005
Statistical plan date	Not stated
Study dates	11/21/2003 to 6/28/2006
Inclusion criteria	Male or female 55 to 90 years of age Clinical diagnosis of dementia according to DSM-IV and: 1. ICC probable or possible for DLB 2. NINCDS-ADRDA for AD, or 3. NINDS-AIREN for VaD, and: 4. Mini mental state examination score ≥ 10
Main exclusion criteria	1. Diagnosis of PD 2. Pregnancy 3. Past cerebral infarction in region of basal ganglia 4. Severe depression 5. Normal pressure hydrocephalus 6. Interfering medications (does not include dopamine agonists and antagonists)
Primary endpoints	Sensitivity and specificity of DaTSCAN visual assessment (BIE) in differentiation between patients with "Probable" DLB

	versus non-DLB dementia (using baseline CP clinical diagnosis as SOT).
Secondary endpoints	<ol style="list-style-type: none"> 1. Re-evaluation of the primary and secondary efficacy endpoints via the 12 month re-assessment of the clinical diagnosis 2. Accuracy, PPV, NPV based on the dichotomous visual read (BIE) compared to the clinical diagnosis given by an independent CP from a documented assessment. 3. Assessment of Datscan ability to increase investigator performance and confidence in differential diagnosis of DLB and other types of dementia and to assess clinical usefulness of management decisions for subjects with DLB. The accuracy and sens/spec of the on-site investigator's baseline diagnosis will be compared to those of the investigator's post- Datscan diagnosis. 4. Summary of the proportions of abnormal/normal Datscan SPECT visual reads (BIE) in relation to the groups of probable DLB, possible DLB, and non-DLB 5. Semi-quantitative analysis of Datscan images: comparison of striatal uptake ratios between the 3 groups of probable, possible and non-DLB dementia
Safety endpoints	<p>Proportion of subjects with 1 or more treatment-emergent AEs; Any clinically significant changes from baseline in clinical assessments (PE, EKG, vital signs, labs);</p> <p>Safety evaluation was not part of the 12-month follow-up</p>
Standard of truth	Clinical diagnosis by consensus panel (3 DLB experts) at T=0 (primary efficacy measurement) & reassessment at T=12 months
Statistical thresholds for success	Sensitivity – 65%, Specificity – 73%
Clinical diagnosis method	Established by an independent, off-site

	<p>consensus panel of 3 DLB experts by review (no physical examination) of all available clinical data (laboratory and prior imaging results, excluding Datscan imaging results) from the study site, including on-site investigator's clinical diagnosis, and based on the following diagnostic criteria:</p> <p>Alzheimer's Disease: NINCDS-ADRDA criteria (published in Neurology, 1984)</p> <p>Dementia with Lewy Bodies: International Consensus Criteria (ICC) for the diagnosis of DLB (report of the consortium on DLB international workshop, published in Neurology, 1996)</p> <p>Vascular Dementia: National Institute of Neurological Disorders and Stroke - Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN)</p>
Image analysis method	Blinded image evaluation by 3 independent nuclear medicine physicians at image review center in Oslo, Norway
Image acquisition method	<p>All cameras were capable of SPECT imaging.</p> <p>Reconstruction methods were not defined in the protocol and may have varied by study site.</p>
Prespecified efficacy thresholds	Sensitivity greater than 65% and specificity greater than 73%
Disease severity of patients at baseline	Not enough information to assess
Disease severity of patients completing 12 month follow-up assessment (PPP) (N=235)	<p>Not enough information to assess in detail.</p> <p>At 12 month f/u, clinical diagnoses were:</p>

	DLB Probable DLB – 86 (37%) Possible DLB – 25 (11%) AD Probable AD – 84 (36%) Possible AD – 29 (12%) VD Probable VaD – 1 (<1%) Possible VaD – 9 (4%)
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Study PDT301 was originally designed to determine the sensitivity and specificity of the visual assessment of Datscan SPECT images in differentiating between “probable DLB” and “non-DLB” subjects as determined by the clinical diagnosis (SOT), established by an independent consensus panel (CP) at baseline and after the 12-month follow-up. The clinical diagnosis was established by published consensus criteria (1996 criteria) for DLB diagnosis, and was based on all clinical and neuropsychiatric data collected during the study period, without knowledge of Datscan imaging results.

The revised objective for the U.S. study report was stated as:
 “To determine, in subjects with symptoms and signs of dementia, the sensitivity and specificity of the visual assessment of Datscan SPECT images in detecting or excluding a SDD. The presence of a SDD was indicated by a SOT diagnosis of DLB, and the absence of a SDD was indicated by a SOT diagnosis of another form of dementia (AD or VaD) that is not associated with a SDD.”

The clinical diagnoses (SOT) were designated as probable DLB, possible DLB and non-DLB. These diagnoses were then compared to the blinded image evaluations to determine sensitivity and specificity for detecting or excluding SDD. Measurements of sensitivity and specificity were performed with the “probable DLB” compared to non-DLB, as well as including the “possible DLB” group in the efficacy analysis.

Reviewer’s Comments:

PDT301 was designed to determine the diagnostic performance (sens/spec) of DaTSCAN in differentiating between “Probable” DLB subjects and non-DLB dementia subjects. Clinical diagnoses were categorized as probable DLB, possible DLB, or non-DLB by the off-site consensus panel (3 DLB experts) based on the 1996 published consensus criteria for DLB diagnosis. The CP had knowledge of the on-site investigator’s baseline clinical diagnosis and reviewed all available clinical data, including prior imaging examinations (excluding DaTSCAN results). Multiple statistical analyses were then performed using the blinded image reads compared to different combinations of these clinical diagnosis (SOT) categories. This method of determining sensitivity and specificity using “probable” DLB and excluding “possible” DLB has the

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potential to confound efficacy measurements. For the primary efficacy analysis, “probable” DLB and non-DLB will be compared to the blinded image reads.

It should also be noted that dopamine agonists and antagonists were allowed as concomitant medications in the trial. The applicant has not submitted human data to support the claim that dopamine agonists and antagonists do not alter the DaT protein distribution in the striatum or Datscan image results.

Of greater importance, baseline clinical diagnosis is not an acceptable SOT for DLB, as long follow-up is needed to make this clinical diagnosis. Even with longer follow-up, a definitive diagnosis of DLB cannot be made (see FDA neurology consult in DARRTS by Dr. Gerald D. Podskalny, page 5 of 17). It is unusual that the sponsor would utilize 36 month follow-up to establish clinical diagnosis for the study in early Parkinsonian subjects (304), but only baseline clinical diagnosis for DLB subjects.

Additionally, the clinical diagnosis was determined using the 1996 consensus criteria for the diagnosis of DLB. The 1996 consensus criteria are thought to have suboptimal sensitivity for making the DLB diagnosis. New consensus criteria (clinical and pathologic) for DLB diagnosis were published in 2005 and are thought to improve the diagnostic accuracy of the clinical diagnosis and pathological confirmation of DLB. (Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium, Neurology, 65:1863-1872). Therefore, the use of clinical diagnosis as a SOT undermines the reliability of efficacy results for study 301. In this reviewer’s opinion, study 301 does not qualify as a confirmatory study to support the use of DaTSCAN in subjects with dementia.

Table 6: Study 304

Study 304	
Design	Phase 3, multi-center (10 centers), open-label, non-randomized study to determine the predictive value of Datscan SPECT in differentiating between subjects with early features of Parkinsonism, other causes of tremor (ET) and healthy volunteers
Protocol date (Original)	11/16/1998
Amendments to protocol	12/21/1998 07/01/1999, 10/04/1999, 08/14/2000, 04/12/2001, 06/27/2001, 12/07/2001, 07/26/2002, 04/28/2004, 08/05/2005

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Statistical plan date	Not stated
Study dates	1/18/1999 to 6/28/2005
Inclusion criteria	<p>Subjects with early features of Parkinsonism:</p> <ol style="list-style-type: none"> 1. Male or female 30 to 90 years of age 2. Cardinal features of Parkinsonism 3. Unified Parkinsons Disease Scale (UPDRS) part III scoring ≤ 16 <p>Healthy volunteers:</p> <ol style="list-style-type: none"> 1. Male or female 30 to 90 2. Good age-appropriate health as established by clinical examination
Exclusion criteria	<ol style="list-style-type: none"> 1. History of stroke or cerebral vascular 2. Disease 3. Psychiatric illness other than depression 4. Positive for dementia by DSM IV-R 5. History of repeated head injury 6. History of definite encephalitis 7. Neuroleptic treatment at onset of symptoms or MPTP exposure 8. Features suggestive of MSA or PSP 9. History of response to drug therapy suggested idiopathic PD, > 5 year history
Primary endpoints	Sensitivity and specificity of DaTSCAN images (BIE) in differentiating between "Probable" or "Possible" PD versus non-PD (using the SOT assessment at 36 months).
Secondary endpoints	<ol style="list-style-type: none"> 1. Institutional visual read of Datscan images at T=0 compared to clinical diagnosis by blinded, institutional neurologist at T=3 months. 2. Sens/spec, accuracy, PPV, NPV for the institutional read and the BIE reads at T=0 compared to the clinical diagnosis established by 2 independent MDS at T=18 and T=36 months. 3. Sens/spec, accuracy, PPV and NPV for the institutional, clinical diagnosis at T=0

	<p>compared to the 2 independent, MDS diagnoses at T=18. Same analyses also performed for the institutional clinical diagnosis at T=0 compared to the consensus diagnosis by the 2 independent MDS at T=36.</p> <p>4. Exploratory analyses of the groups of probable PD, possible PD, and non-PD as determined in the IIE video assessment.</p> <p>5. The confidence levels of the clinical diagnosis of idiopathic Parkinson’s Disease.</p> <p>6. Sens/spec, accuracy, NPV, and PPV for the independent SPECT readers at T=0 compared to on-site clinical diagnosis at T=18 and T=36.</p> <p>7. Analysis of the stability of Datscan SPECT findings (institutional visual read and independent SPECT read) over time: sens/spec, accuracy, PPV, NPV for both the institutional read and the independent BIE reads at T=18 and T=36 compared to the consensus diagnosis by 2 independent MDS at T=36 months.</p> <p>8. Inter-reader agreement between Datscan SPECT readers and inter-reader agreement between independent video readers.</p>
Safety endpoints	Only AEs were analyzed for the U.S. CSR
Standard of truth	Consensus diagnosis by 2 movement disorder specialists by review of taped video assessment performed at T=36 months
Diagnostic criteria utilized for consensus diagnosis	<p>Parkinson’s Disease</p> <p>1. Brain Bank Criteria</p> <p>(“Probable” and “Possible” Parkinson’s Disease were grouped together and both considered PD; ET and “other” were considered as non-PD)</p>
Image analysis method	BIE by 3 independent readers a (b) (6) in

	<p>(b) (4) (background not given, but readers were trained by sponsor in Datscan interpretation)</p> <p>(1 institutional read also performed)</p>
Image acquisition method	<p>All cameras were capable of SPECT imaging.</p> <p>Reconstruction methods were not defined in the protocol and may have varied by study site.</p>
Primary statistical hypotheses	None stated
Disease severity of patients at 36 month follow-up SOT assessment (N=102)	<p>Not enough information to assess in detail.</p> <p><u>UPDRS scores (means):</u></p> <p>“Probable” PD group - 20.3 Non-PD group - 7.1</p> <p><u>Diagnoses:</u></p> <p>Parkinson’s Disease Probable PD - 66 (65%) Possible PD - 5 (5%)</p> <p>Non PD – 31 (30%)</p>
Disease severity of patients at baseline pre-dose clinical assessment (N=102)	<p>Not enough information to assess in detail.</p> <p><u>UPDRS scores (means):</u></p> <p>“Probable” PD group - 10.8 Non-PD group - 6.4</p> <p><u>Diagnoses:</u></p> <p>Parkinson’s Disease Probable PD - 44 (43%) Possible PD - 37 (36%)</p> <p>Non PD – 21 (21%)</p>

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Study PDT304 was originally designed to determine the predictive value of Datscan SPECT imaging in differentiating between subjects with early features of Parkinsonism, other causes of tremor (mainly ET), and healthy volunteers. The clinical diagnosis (SOT) was determined by review of taped video assessment (performed at T=18 months and T=36 months) by 2 movement disorder specialists. The primary endpoints

in the European study report were sensitivity, specificity, accuracy, PPV and NPV for both the 1) onsite DaTSCAN image read, and 2) the BIE of DaTSCAN images by 3 independent readers at the (b) (4), as compared to the SOT at T=36 months.

The revised primary endpoints for the U.S. study report were stated as:

“In the reanalysis for the U.S. CSR, sensitivity and specificity for the detection or exclusion of a SDD will be the focus of discussion. The clinical diagnosis established at 36 months was used as the SOT (surrogate for SDD detection). Subject groups were defined as: 1) “Probable” PD, 2) “Possible” PD, 3) Non-PD (ET), and 4) Other. Sensitivity and specificity for the visual image assessments for detecting or excluding a SDD were determined for the following comparisons: 1) “Possible” or “probable” PD vs. non-PD (Primary efficacy analysis), 2) “Probable” PD (SDD present) vs. non-PD (absence of SDD), and 3) “Probable” PD vs. “Possible” PD or non-PD.” The applicant then states in the U.S. study report that these comparisons were done for the on-site clinical diagnosis and separately for the T=36 SOT evaluation, using both the BIE results and the on-site DaTSCAN read.

Reviewer’s Comments:

Study PDT304 is acceptable with regards to study design and the population of subjects (early PS) likely reflects the population of patients to benefit most from Datscan imaging. The drop-outs which occurred over the course of the 36 months follow-up period did not significantly change the patient demographics when comparison is made between the 36 month follow-up (efficacy) population and the baseline population of subjects.

For the primary efficacy analysis, the sponsor evaluated “probable” or “possible” PD versus non-PD to determine the diagnostic performance. There was a pre-specified statistical analysis plan, pre-specified endpoints, and the SOT and image analysis protocols are acceptable. However, there were no pre-defined statistical success thresholds for this study, which is the preferred method for conducting a confirmatory clinical trial.

It should be noted that dopamine agonists and antagonists were again allowed as concomitant medications in the trial. As stated in the comments for study PDT301 the applicant has not submitted human data to support the claim that dopamine agonists and antagonists do not alter Datscan image results.

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Table 7: Study 003

Study 003	
Design	Phase 3, multi-center (6 centers), open-label, non-randomized study to determine the sensitivity and specificity of striatal uptake of Datscan in patients with a documented clinical diagnosis of PD, MSA, PSP or definite ET
Protocol date	11/27/1997
Amendments	07/09/1997, 07/15/1997, 09/17/1997, & 11/27/1997
Statistical plan date	Not stated
Study dates	8/25/1997 to 2/24/1998
Inclusion criteria	<p>Patients:</p> <ol style="list-style-type: none"> 1. PD, MSA or PSP and satisfaction of the UK Parkinson's Disease Society Brain Bank criteria step 1, or 2. ET and satisfaction of the Findley & Koller definite ET definitions <p>Healthy Volunteers: Male and females 50 to 80 years</p>
Exclusion criteria	<p>General:</p> <ol style="list-style-type: none"> 1. Use of prohibited medications (including anti-Parkinson's disease therapy) 2. > 15 mSV/year occupational exposure to radiation 3. History of substance abuse 4. Abnormal lab values deemed clinically relevant by investigator 5. Females of child bearing potential not on birth control 6. Pregnant/lactating females <p>PD patients:</p> <ol style="list-style-type: none"> 1. Evidence of CVD, brain tumor or

	<p>communicating hydrocephalus 2. Positive DSMv IVR assessment for dementia 3. History of repeated stroke or head injury 4. History of definite encephalitis</p> <p>Please see protocol for additional PD, MSA, PSP and ET specific exclusion criteria (pages 31-32)</p>
Primary endpoints	Sensitivity and specificity in differentiating between PS (SDD) and non-PS (ET, no-SDD) based on institutional read of DaTSCAN compared with clinical diagnosis
Secondary endpoints	<p>1. Blinded, consensus read of DaTSCAN images compared to clinical diagnosis, only subjects with “consensus” read were included.</p> <p>2. Analysis of quantitative assessments of region of interest data.</p>
Safety endpoints	AEs, labs, EKG, vital signs
Standard of truth	Pre-existing, documented clinical diagnosis confirmed at baseline by on-site study investigators
Diagnostic criteria utilized for baseline clinical diagnosis	<p>PD:</p> <p>1. Documented diagnosis of PD and satisfaction of UKPDS Brain Bank criteria step 3 2. Documented evidence of positive challenge test to dopamine</p> <p>MSA:</p> <p>1. Documented diagnosis of MSA 2. Satisfaction of the Consensus Committee of the American Autonomic Society and the American Academy of Neurology diagnosis criteria (Neurology 1996;46:1470)</p>

	PSP: 1. Documented diagnosis of PSP 2. Satisfaction of the NINDS-SPSP clinical criteria for diagnosis (Neurology 1996;47:1-9) ET: 1. Documented diagnosis of ET 2. Satisfaction of Findley & Koller definite essential tremor definitions and behavioral classifications for clinical diagnosis (Findley & Koller 1994)
Image analysis method	On-site image analysis by study investigators (Consensus blinded read also performed by 5 of the 13 study investigators, including 1 neurologist & 4 nuclear medicine physicians. Agreement between 3 of 5 readers was considered the “consensus” for that subject.)
Image acquisition method	All cameras were capable of SPECT imaging. Reconstruction methods were not defined in the protocol and may have varied by study site.
Number of subjects: Received study drug Evaluable for safety	224 224
Statistical hypotheses	None
Disease severity of patients	Not enough information to assess

Study DP008-003 was originally designed to determine the sensitivity and specificity of striatal uptake of DaTSCAN in patients with a documented clinical diagnosis of Parkinson’s disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP) compared with essential tremor (ET) and healthy volunteers. The primary endpoint was stated in the European study report as “The primary efficacy variable was identified as the visual assessment of DaTSCAN striatal uptake as determined by the institutional read (clinical diagnosis of the patient by the study site).”

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The European study report also states “Secondary efficacy variables were identified as the visual assessment of DaTSCAN uptake as determined by the blinded read (consensus diagnosis of panel of reader, blinded to the clinical diagnosis, which was derived from the patient’s visual image alone).”

The revised primary endpoints for the U.S. study report were sensitivity and specificity of the on-site institutional read of Datscan SPECT images in differentiating between subjects with Parkinsonian Syndromes (PS), indicating presence of SDD, and non-PS (no SDD present) using the clinical diagnosis as the SOT.

Reviewer’s Comments:

Study DP008-003 was designed to assess the diagnostic performance of DaTSCAN in patients with an established clinical diagnosis of PD, MSA, PSP or ET. Disease severity and duration of symptoms for patients enrolled was not described in the study report. However, patients enrolled had a documented, clinical diagnosis of PD, MSA, PSP or ET. Therefore, it is reasonable to conclude the patients in this study were more advanced in their disease stage than patients in study PDT304, which also enrolled PD and ET patients.

There are additional review concerns for this study. These include lack of pre-specified statistical thresholds for success. Also, the documented, on site clinical diagnosis verified by study investigators is not an acceptable SOT, as it is subject to investigator bias. The on site image evaluation is also subject to bias. It is not clear if the on-site institutional readers were blinded, or had access to patient identity and/or clinical information during the institutional image evaluation. For the efficacy analysis, data comparing the blinded read to clinical diagnosis will be considered. The blinded “consensus” read was performed by 5 of the study investigators at the Amsterdam study site. A “consensus” was defined as agreement between 3 of 5 readers for a given subject’s images. “Mismatches” between DaTSCAN consensus image read results and clinical diagnoses were followed up with the individual study sites, but neither the baseline clinical diagnoses (SOT) nor the DaTSCAN consensus reads were changed following the mismatch analyses.

In contrast to studies PDT301 and PDT304, all anti-Parkinson’s disease therapy was withdrawn (time period decided on case by case basis) prior to subject initiation in this study.

This reviewer’s opinion regarding DP008-003 is that it is not acceptable as a confirmatory study, but provides supportive data for DaTSCAN use in patients with Parkinsonian disorders.

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Table 8: Walker Study

Walker Study	
Design	Investigator initiated, single center, proof of concept, open-label, non-randomized, cross-sectional and longitudinal study to investigate changes in the dopamine transporter using Datscan SPECT in subjects with DLB, other dementias and PD
Protocol date	Not stated
Amendments	None
Statistical plan date	Not stated
Study dates	6/1996 to 12/1999 (autopsy phase ongoing)
Inclusion criteria	Subjects meeting one of the following: <ol style="list-style-type: none"> 1. AD meeting the NINCDS/ADRDA criteria 2. PD meeting UK Parkinson's Disease Brain Bank criteria 3. DLB meeting the International Consensus Criteria for DLB (1996 criteria) 4. Healthy control subjects, age matched, not taking drugs known to affect the dopaminergic system
Exclusion criteria	Not stated
Primary endpoints (Longitudinal stage for U.S. study report)	Sensitivity and specificity of Datscan images compared to neuropathological diagnosis at autopsy
Secondary endpoints	Baseline clinical diagnosis compared to neuropathological diagnosis at autopsy (ROI-based semi-quantitative analysis of DaTSCAN striatal uptake ratios compared

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	to neuropathological diagnosis was also performed)
Safety endpoints	Spontaneously reported adverse events collected
Standard of truth	Blinded neuropathological diagnosis at autopsy
Baseline clinical diagnosis method	<p>Established by 1 clinician (on-site study investigator) at baseline based on fulfillment of the below criteria:</p> <p>Alzheimer's Disease: 1. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), published in Neurology, 1984.</p> <p>Dementia with Lewy Bodies: 1. Consensus DLB criteria (report of the consortium on DLB international workshop, published in Neurology, 1996)</p> <p>Parkinsons Disease: 1. UK Parkinson's Disease Society Brain Bank Criteria (Hughes et al 1992)</p>
Image analysis method	Blinded image evaluation based on consensus of 3 on-site readers (exception: 1 reader had access to patient identity & clinical information during the study, but did not review this information during image assessments)
Image acquisition method	A dedicated brain SPECT camera (Strichman Medical Equipment 810 linked to Macintosh computer) was used for all scans. Reconstruction method not defined.
Primary statistical hypotheses	None stated

<p>Disease severity of patients at time of DaTSCAN imaging (baseline)</p>	<p>Not enough information to assess in detail.</p> <p>Average age of dementia onset: 73.6 years (range: 53 – 93)</p> <p>Average age at DaTSCAN imaging: 77.5 years (range: 58 – 95)</p> <p>Average time from onset of dementia to DaTSCAN imaging: approximately 4 years</p> <p>(Subjects with DLB had higher dementia scores than non-DLB subjects)</p>
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The Walker study is an ongoing investigator-initiated study being conducted in the UK (12 investigators), and the only study to use neuropathological diagnosis at autopsy as the standard of truth. It was originally designed to investigate the pre and post-synaptic components of the striatal dopaminergic system (caudate/putamen radioactivity ratios) of patients diagnosed with DLB and to compare them with AD, PD patients and healthy controls. The applicant has utilized preliminary data from this study to determine the sensitivity and specificity of Datscan SPECT images in confirming the established clinical diagnosis of DLB patients.

Reviewer’s Comments:

The Walker study is a small sample of patients which utilizes the optimal standard of truth of autopsy histopathology to confirm the clinical diagnosis. However, there were no measurements performed on the human brain slices to confirm binding of DaTSCAN to the DaT protein.

Although blinded image reads were performed by 2 of the 3 readers, one reader had access to clinical information throughout the study, including the clinical diagnoses, which introduces some potential bias into the image reads.

The Walker study also used the consensus DLB criteria published in 1996 to determine the neuropathological diagnosis at autopsy and baseline clinical diagnosis. As previously noted, DLB consensus criteria (clinical and pathology) have undergone changes since this time, and new criteria were published in 2005. Also of significant concern are the findings at autopsy of mixed pathology for a majority of subjects in this study. Patients with any findings of DLB at autopsy were classified as DLB, even if they had AD findings at autopsy and/or did not display a clinical picture of DLB. The new consensus criteria for DLB published in 2005 address this issue of mixed pathology for DLB and AD. Under the 1996 consensus criteria used for this study, it is estimated that

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“as many as 60% of AD cases may be considered to meet pathologic criteria for DLB using the 1996 criteria. Virtually none of these patients will have had the DLB syndrome...” (Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium, Neurology, 65:1863-1872).¹

It should also be noted that the longitudinal study phase (patients with autopsy data), the mean age for reported onset of dementia was 73.6 (median 73.5, range 53-93) and the mean age at time of Datscan was 77.5 (median 77.5, range 58-95). Therefore, on average, approximately 4 years passed from the reported onset of symptoms to when patients underwent DaTSCAN imaging. Thus, these patients were more advanced in their disease syndrome than patients initially presenting with dementia symptoms. This finding may undermine the value of efficacy results for this study, as Datscan imaging may be most beneficial in patients who have early signs/symptoms of dementia (or movement disorders), when the clinical diagnosis is difficult to ascertain.

These issues raise major questions regarding the reliability of efficacy measurements in the Walker study, and create significant doubt regarding the accuracy and reliability of data submitted for Datscan in patients with dementia (studies 301 and Walker).

Overall reviewer's comments:

Studies PDT301, PDT304, DP008-003 and the Walker study (longitudinal phase) were all designed to test the diagnostic performance of DaTSCAN SPECT imaging in differentiating between either PS and non-PS or DLB and non-DLB dementia subjects.

The phase 3 studies contain a heterogeneous mix of patient populations, with only partially defined disease severities for the included patients. There were no pre-specified thresholds for statistical success for studies PDT304, DP008-004 or the Walker study, which is the preferred method for conducting confirmatory studies. Furthermore, the SOT was determined based on different methods in each study, with only the Walker study using pathology as a SOT to confirm the clinical diagnosis. Using baseline clinical diagnosis of DLB (based on outdated consensus criteria) as a SOT, as performed in study 301, is not acceptable in this reviewer's opinion.

There are additional questions regarding blinding of the image readers and consistency of image interpretation methods across studies readers (imaging review charters not submitted). In study 003, on-site investigators participated in an unblinded image read. In the Walker study, one of the 3 image readers had access to patient identity and clinical information during the study. The above study design and conduct issues raise concern regarding the reliability of some efficacy measurements presented in the NDA.

There is also concern regarding the effect of dopaminergic medications on Datscan results. Only study 003 excluded subjects on these medications. Previous studies of related compounds (beta-CIT) have shown disagreement between clinical status and Datscan image results in patients receiving dopaminergic medications to treat

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Parkinson's disease at the time of Datscan SPECT imaging, which raises the concern for potential effects of these medications on Datscan performed characteristics.^{6,10}

With regards to the dementia studies, this reviewer's opinion is that no confirmatory studies exist in the NDA to support the reliability and accuracy of Datscan in differentiating between subjects with DLB and non-DLB dementia (AD). Furthermore, the clinical usefulness of Datscan in dementia subjects is doubtful when considering the mixed pathology seen in these patients at autopsy, as the scientific literature reveals most subjects with DLB will have beta amyloid plaque burden which meets AD criteria.⁴¹ Thus, the potential exists to misclassify patients with abnormal Datscan images as DLB, when AD is part of their clinical syndrome.

However, study 304 was adequately designed to measure the reliability and accuracy of Datscan in differentiating between PD and non-PD subjects who present with early signs of Parkinsonism. This study enrolled subjects who most likely reflect the population of patients for which Datscan imaging may be clinically useful. The SOT assessment and image read methods were also acceptable. In this reviewer's opinion, study 304 is an acceptable study to demonstrate the ability of Datscan to provide a reliable measurement of DaT protein distribution in the striatum in this population of patients.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The applicant's original proposed indication was:

Datscan is a radiopharmaceutical containing [¹²³I] ioflupane, indicated for detecting loss of functional nigrostriatal dopaminergic neurons by single photon emission computed tomography (SPECT) imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration.

In review of the pre-clinical and clinical data submitted in this NDA, it was decided Datscan would best fit the indication category of "functional, physiological, or biochemical assessment", under the FDA Guidance for Industry, Developing Medical Imaging Drug and Biological Products, emphasizing the biochemical assessment sub-

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category. In the Advisory Committee briefing document, we proposed the alternate Datscan indication of:

“visualization of the dopamine transporter (DaT) distribution within the striatum by SPECT imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration”.

This indication more accurately reflects the nature of the submitted pre-clinical and clinical data submitted in the NDA, and was accepted by the sponsor as the revised, current proposed indication.

6.1.1 Methods

This efficacy review focuses on the original primary endpoints (sens/spec) and original statistical analysis plans of the phase 3 studies. These study data may be used as support for the clinical usefulness, reliability and accuracy (CFR 21, 315.5) of DaTSCAN for the revised, current indication stated above.

Reviewer’s Comments:

The applicant is not proposing to market DaTSCAN as a diagnostic test for any specific disease or condition. However, the submitted phase 3 efficacy studies were designed to evaluate the diagnostic performance (sens/spec) of DaTSCAN imaging in patients with symptoms or clinical diagnoses of Parkinsonism or dementia.

6.1.2 Demographics

Table 9 shows the baseline characteristics for the intent to diagnose population (ITD) for each study.

Table 9: Demographic Characteristics by Study – ITD.

Study	301 (N= 326)	304 (N= 179)	003 (N=224)	Walker (N=22, longitudinal phase)
Median Age Min, Max,	75 54, 90	63 33, 86	64 40, 80	78 58, 95
Male Female	57% 43%	57% 43%	61% 39%	59% 41%
Race Caucasian Black Asian	100% 0% 0%	98%	98% 1% 1%	Not given

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Reviewer's comments:

The patient populations enrolled in these studies are reflective of the proposed patient population with regards to age and gender. However, there is very little data on Datscan use in minority populations contained in the NDA.

6.1.3 Subject Disposition

Table 10 provides a summary of the subject disposition for each study included in the efficacy analysis.

Table 10: Summary of Patient Disposition by study.

Study	301	304	003	Walker (long. phase)
Enrolled	351	202	250	45
Dosed	326	179	224	45
SOT Evaluated	326	102	224	22
Image Evaluable	313	174	220	45
Efficacy	313	102	220	22
Primary Efficacy Evaluated	231	102	185	22

Table 11 shows the baseline characteristics and diagnoses for the dosed subjects and subjects included in the primary efficacy analysis (36 month follow up available) for study 304.

Table 11: Study 304 baseline characteristics and diagnoses between dosed and efficacy subjects.

	Dosed (Baseline) N=179 n (%)	Efficacy (36 follow-up) N=102 n (%)
Female n (%)	77 (43)	45 (44)
Age ≥ 65 n (%)	77 (43)	42 (41)
Age Median (Range)	63 (33 – 86)	61 (33 – 79)
Caucasian n (%)	176 (98)	102 (100)
Probable Parkinson's	79 (44)	44 (43)

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Possible Parkinson's	55 (31)	31 (30)
Benign Parkinson's Disease	8 (4)	6 (6)
Possible Essential Tremor	22 (12)	14 (14)
Other	15 (8)	7 (7)

Reviewer's Comments:

Study 304 disposition data reveals there were 179 subjects dosed and 174 subjects with evaluable images, but only 102 subjects with SOT evaluated and available for efficacy assessments. This is a largely a result of the 36 month follow-up period required to determine the clinical diagnosis (SOT) of PD or non-PD, and is not unexpected. An analysis of the dosed subjects and efficacy subjects (see table 11) reveals similarity in demographics between these subject groups.

Table 12 shows a summary of the causes for lack of completion within each study.

Table 12: Subject dispositions by Study – Enrolled Population.

	301 (N=351)	304 (N=202)	003 (N=250)	Walker (N=45)
Completed	323 (92%)	98 (49%)	223 (89%)	22
Early Termination	28 (8%)	103 (51%)	27 (11%)	18 (5 being followed)
Reason for Early Termination:				
Subject request/Withdrew consent	16 (5%)	46 (23%)	18 (7%)	10
MD/Sponsor/Investigator Request	2 (1%)	0 (0%)	2 (1%)	
Excluded from Participation	0 (0%)	10 (5%)	0	
Lost to follow-up	2 (1%)	32 (16%)	0	7
Adverse Event	1 (<1%)	0 (0%)	0	
Safety Reason (includes AEs)	0 (0%)	10 (5%)	0	
Protocol violation	3 (1%)	4 (2%)	7 (3%)	
Other	4 (1%)	1 (<1%)	0	1
Evaluated in SPECT BIE	322 (92%)	174 (86%)	223 (89%)	45 (100%)
Excluded from SPECT BIE (images unavailable)	7 (2%)	UNK	3 (1%)	
Evaluable for Efficacy	288 (82%)	102 (50%)	220 (88%)	22
Intent to Diagnose Population (ITD)	326 (93%)	102 (50%)	220 (88%)	45
Per-Protocol Population (PP)	288 (82%)	100 (50%)	157 (63%)	22

Table 13 provides a summary of protocol violations for each study.

Table 13: Major Protocol Violations by Study – Dosed Population.

	301 (N= 326)	304 (N=179)	003 (N=224)	Walker (N=45)
Main Study Violations				
Administered prohibited meds	0	0	0	Not available
Inclusion/Exclusion criteria	9 (3%)	2 (1%)	23 (10%)	
Study Procedures	0	4 (2%)	54 (25%)	
Follow-up Study Violations				Not available
Inclusion/Exclusion criteria	0	0	0	
Study procedures	0	0	4 (2%)	

Reviewer’s comments:

As seen in table 13, study 003 had the most protocol violations, with 66 subjects (44 PS, 13 ET, 9 HV) revealing 77 violations. These violations were related to inclusion/exclusion criteria (n=23 violations) and study procedures (54 violations). The violations related to study procedures were mainly due to subjects receiving > 5 mCi Datscan. These subjects were excluded from the PP population.

Table 14 shows the clinical diagnoses for subjects in each study as determined by the standard of truth assessments.

Table 14: Summary of Clinical Diagnoses (per SOT) by study.

Study	301 (N=242)	304 (N=102)	003 (N=220)	Walker (N=22)
Parkinsonian Syndrome (PS; SDD)	0	71 (70%)	158 (72%)	0
Possible PS	0	5 (5%)	158 (72%)	
Probable PS	0	66 (65%)		
Dementia with Lewy Bodies (DLB; SDD)	116 (36%)	0	0	14 (67%)
Possible DLB	27 (8%)	0	0	
Probable DLB	89 (27%)	0	0	
Non-PS/Non-DLB (No SDD)	126 (39%)	31 (30%)	62 (28%)	8 (33%)
ET	0 (0%)	14 (14%)	27 (12%)	
AD	125 (38%)	0	0	
Other	1 (<1%)	17 (17%)	35 (16%)	

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SDD Present	116 (48%)	71 (70%)	158 (72%)	14 (64%)
SDD Absent	126 (52%)	31 (30%)	62 (28%)	8 (36%)

6.1.4 Analysis of Primary Endpoint(s)

The original primary efficacy endpoints for studies PDT301, PDT304, DP008-003 were sensitivity and specificity of Datscan visual image interpretations compared to the clinical diagnosis as the SOT. Although initially not clearly defined, sensitivity and specificity compared to neuropathology at autopsy were the primary efficacy endpoints in the U.S. study report for the Walker study.

Each image assessment was classified as a true positive (TP), true negative (TN), false positive (FP), or false negative (FN). These data were then used to calculate the sensitivity and specificity.

Sensitivity was defined as: $\frac{nTP}{nTP + nFN}$

Specificity was defined as: $\frac{nTN}{nTN + nFP}$

Movement disorder studies (PDT304 and DP008-003)

For these tables, the primary efficacy was based on blinded image reads compared to the SOT assessment. For DP008-003, the blinded reads were not part of the primary efficacy analysis as defined in the study protocol.

As seen in table 15, the point estimate for sensitivity of Datscan images in differentiating between early Parkinsonism and other forms of tremor (non-Parkinsonism) was approximately 78%. The point estimate for specificity was 96% for all 3 readers.

Table 15: Study 304 sensitivity and specificity of Datscan in early Parkinsonism subjects.

	Sensitivity (95% CI)	Specificity (95% CI)
Reader A N=102	77.5 (66.0, 86.5)	96.8 (83.3, 99.9)
Reader B N=99	77.9 (66.2, 87.1)	96.8 (83.3, 99.9)
Reader C N=101	78.6 (67.1, 87.5)	96.8 (83.3, 99.9)

As seen in table 16, the point estimate for sensitivity of Datscan images in subjects with an established clinical diagnosis of PS (PD, PSP, DLB) versus non-PS (mainly ET) ranged from 92% to 97%. The point estimate for specificity ranged from 74% to 96%.

Table 16: Study 003 sensitivity and specificity of Datscan in subjects with documented clinical diagnosis of PD, PSP, MSA or ET.

	Sensitivity (95% CI)	Specificity (95% CI)
Reader A N=185	93.0 (87.9, 96.5)	96.3 (81.0, 99.9)
Reader B N=185	96.8 (92.8, 99.0)	74.1 (53.7, 88.9)
Reader C N=185	96.2 (91.9, 98.6)	85.2 (66.3, 95.8)
Reader D N=185	92.4 (87.1, 96.0)	92.6 (75.7, 99.1)
Reader E N=185	94.3 (89.5, 97.4)	92.6 (75.7, 99.1)

Reviewer’s comments:

Patients enrolled in study 003 had a documented, clinical diagnosis of PD, MSA, PSP or ET. Therefore, these patients were more advanced in their disease stage than the patients in study PDT304 (early PD and ET patients). This likely explains (at least partially) the higher sensitivity results obtained for study 003 compared to study 304. Over a period of years, true PD patients should reveal themselves and fulfill the clinical criteria for diagnosis. Furthermore, Datscan images should reveal abnormal signal in the striatum in patients who have been followed for years and fulfill the criteria for a PD diagnosis. The population of patients in study 003 likely does not reflect patients most likely to benefit from Datscan imaging, which are those with early Parkinsonism (such as study 304 patients). However, the observation that sensitivity of Datscan improves as patients progress from early Parkinsonism (study 340) to a documented diagnosis of either IPD, PSP, or MSA may strengthen the evidence in support of Datscan in patients with a Parkinsonian syndrome. In this reviewer’s opinion, study 304 and 003 results provide a reasonable representation of agreement between Datscan images and clinical status in patients suspected of having or clinically diagnosed with Parkinsonian syndromes.

In study 304, five of the seven (71%) subjects designated as “true false negatives” were receiving anti-Parkinson’s medication. The sponsor has not submitted data to support the claim that dopamine replacement therapy will not affect Datscan image findings. This issue is of significant concern and should be addressed in future clinical studies of Datscan.

Dementia studies (PDT301 and Walker)

For these tables, the primary efficacy was based on blinded image reads compared to the SOT assessment.

Table 17 shows the sensitivity point estimates of Datscan images in differentiating between “Probable” DLB and non-DLB dementia ranged from 75% to 80% for the 3 central, blinded readers. Specificity point estimates ranged from 89% to 91%. Of note, subjects classified as “Possible” DLB were not included in this analysis.

Table 17: Study 301 sensitivity and specificity of Datscan in subjects with clinical diagnosis of dementia.

	Sensitivity (95% CI)	Specificity (95% CI)
Reader A N=216	79.8 (69.2, 88.0)	91.2 (85.2, 95.4)
Reader B N=216	75.3 (64.2, 84.4)	88.5 (82.0, 93.3)
Reader C N=218	80.3 (69.9, 88.3)	90.5 (84.3, 94.9)

Table 18 shows the mean sensitivity point estimate (3 on-site readers) of DaTSCAN images in diagnosing DLB and AD (compared to pathology) was 78% and the specificity point estimate was 85%. The mean sensitivity of the baseline clinical diagnosis for DLB was 78% and the specificity was 46%.

Table 18: Walker study sensitivity and specificity for baseline clinical diagnosis and Datscan images compared to neuropathology.

	Sensitivity (95% CI)	Specificity (95% CI)
Baseline clinical diagnosis N=22	77.8 (40.0, 97.2)	46.2 (19.2, 74.9)
DaTSCAN N=22	77.8 (40.0, 97.2)	84.6 (54.6, 98.1)

Reviewer’s comments:

The numerical point estimates for sensitivity and specificity of Datscan in study 301 and the Walker study are similar, but the confidence intervals are notably wider in the Walker study, partially related to the small sample size (n=22). In the Walker study, the performance of the baseline clinical diagnosis was not optimal, and the specificity was notably lower than the specificity for Datscan imaging. The clinical and pathological diagnosis of DLB were based on 1996 consensus criteria (revised in 2005). As stated in the Walker study reviewer comments, under the old consensus criteria, it is postulated that up to 60% of AD patients could be wrongly categorized as DLB patients based on pathology findings, even if these patients never exhibited the DLB clinical syndrome. This issue and the use of only 1 on-site study clinician to determine the

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baseline diagnosis may account for the low performance of the Walker study baseline clinical diagnosis. This finding casts significant doubt on the accuracy of efficacy measurements in study 301 based on the SOT of baseline clinical diagnosis.

6.1.5 Analysis of Secondary Endpoints(s)

Movement disorder subjects (Study 304)

Table 19 provides results of a secondary efficacy analyses for study 304. Shown are the sensitivity and specificity point estimates of DaTSCAN central, blinded reads compared to the SOT clinical diagnosis performed at T= 18 months.

Table 19: Sens/spec of Datscan BIE reads compared to T= 18 months SOT.

Study 304	Sensitivity % (95% CI)	Specificity % (95% CI)
Video reader 1		
BIE Reader A N= 128	67.0 (56.9, 76.1)	75.0 (55.1, 89.3)
BIE Reader B N= 125	67.0 (56.7, 76.2)	75.0 (55.1, 89.3)
BIE Reader C N= 127	67.7 (57.5,76.7)	75.0 (55.1, 89.3)
Video Reader 2		
BIE Reader A N= 125	70.5 (60.3, 79.4)	83.3 (65.3, 94.4)
BIE Reader B N= 122	69.6 (59.1, 78.7)	80.0 (61.4, 92.3)
BIE Reader C N= 124	71.3 (61.0, 80.1)	83.3 (65.3, 94.4)

Reviewer's comments:

When compared to table 15 (T=36 month SOT), it is clear the diagnostic performance of Datscan improved when utilizing the T= 36 months SOT assessment compared to the T= 18 months SOT assessment. This is likely explained by a more accurate clinical diagnosis performed at 36 months of follow-up compared to 18 months.

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Dementia subjects (Study 301)

Table 20 gives results of a secondary analysis for study PDT301 with the diagnostic differentiation of “probable” or “possible” DLB versus Non-DLB dementia.

Table 20: Study 301 sensitivity and specificity for “Probable” or “Possible” DLB vs. Non-DLB dementia.

	Sensitivity % (95% CI)	Specificity % (95% CI)
Reader A N=269	64.4 (55.6, 72.5)	91.2 (85.2, 95.4)
Reader B N=268	60.5 (51.5, 69.0)	88.5 (82.0, 93.3)
Reader C N=273	61.8 (53.1, 70.0)	90.5 (84.3, 94.9)

Reviewer’s comments:

When comparing the sensitivity results from table 20 to table 17, it is clear that sensitivity results are notably lower when the “possible DLB” group is included in the analysis for study 301. The lower sensitivity seen when “possible DLB” and “probable DLB” are combined in the analysis indicates that Datscan may not have adequate sensitivity in subjects with early signs of DLB, as the lower range of the confidence intervals in the above table approach 50% (flip of a coin). Conceptually, this may be explained (at least partially) by DLB patients having a loss of DaT protein that is not above the threshold (unknown) for Datscan detection. The scientific literature reports that DLB subjects have less dopaminergic depletion at presentation compared to Parkinsonian subjects, which may support the above reasoning and findings.

These results combined with the inadequate use of baseline clinical diagnosis of DLB (see reviewer’s comments in 5.3, under table 5) as a SOT raise significant doubt regarding the reliability of Datscan in measuring the DaT protein distribution in the striatum in dementia subjects. In this reviewer’s opinion, the sponsor has not provided sufficient evidence of Datscan effectiveness, (clinical usefulness, accuracy and reliability) as described in CFR 21, 315.5, for use in this patient population.

6.1.7 Subpopulations

No specific subpopulations were identified that resulted in differences in efficacy measurements.

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Overall reviewer comment regarding efficacy:

Following evaluation of the entire efficacy profile for the product, this reviewer concludes that study 304 was adequately designed and provides reasonable estimates of accuracy and reliability for Datscan imaging in subjects with early Parkinsonism. Study 003 also provides supportive evidence for Datscan clinical usefulness in subjects with Parkinsonism.

This reviewer's opinion is the NDA does not contain confirmatory data as described in the FDA radiopharmaceutical regulations (CFR 21, 315.5) to support the effectiveness of Datscan in measuring striatal DaT distribution in subjects with dementia.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Clinical information obtained after a single, intravenous injection of Datscan

Study CY 95.FP.I (single dose of Datscan, 3 mCi)

- 95% clearance of Datscan administered dose from the blood within 5 minutes post-injection, with 98% clearance after 15 minutes post injection.
- Blood activity remained stable beyond 5 hours post-injection, decreasing to approximately 1% of the injected dose within 48 hours post-Datscan injection.
- 60% of administered dose was eliminated in the urine at 48 post-Datscan injection.
- Brain radioactive uptake was approximately 7% of administered Datscan dose, with 30% of this concentrated in the striatum.
- Highest levels of radioactivity were measured in the lungs, liver and brain.
- Radiation dose estimates revealed an average effective dose equivalent of 0.024 mSv/MBq, or 2.66 mSv for a 3 mCi injection of Datscan.

Study CY 96.FP.II (single dose of Datscan, 3 mCi)

- Following SPECT imaging at multiple time points, ratios of specific (striatal) binding to non-specific binding were found to be stable between 3 and 6 hours post-Datscan administration.

Phase 3 development program

All sponsor initiated phase 3 studies utilized a Datscan dose of 3-5 mCi by intravenous injection. Most subjects received a single dose of Datscan, with a smaller number of subjects (study 304) receiving multiple doses of Datscan over long follow-up periods.

- Estimated radiation effective dose is calculated to be approximately 4 mSv for a 5 mCi single administration of Datscan.

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Reviewer's comments:

The above phase 1 and 2 studies provided the basis for the proposed single dose of 3-5 mCi of Datscan by intravenous administration. The sponsor did not conduct any dose ranging studies prior to initiating the phase 3 program. Pharmacokinetic parameters were not investigated in subgroups of patients with different baseline medical histories (renal/hepatic failure) or for different baseline demographic characteristics.

Phase 3 studies were conducted base on the above studies revealing SPECT imaging was feasible, allowing visual and semi-quantitative analyses of Datscan images, and with acceptable dosimetry results, following administration of a single 3 mCi Datscan dose. Clinical studies have been conducted with dose ranges of 3.3 to 7.8 mCi, but no evidence of increased efficacy in the upper dose ranges exists. Therefore, the dose limit of 5 mCi was somewhat arbitrarily chosen by the sponsor.

7 Review of Safety

Safety Summary

Safety data for Datscan from 8 clinical studies (n=942 subjects) and post-marketing data from 2000-2009 reveal no important safety signals for Datscan administration. There have been no deaths or serious adverse events attributable to DaTSCAN as determined by the study investigators. In addition, data from clinical laboratory evaluations, vital sign monitoring and ECG assessments have produced no important concerns regarding Datscan use.

7.1 Methods

The applicant has submitted safety data from nine studies, with a total of 942 subjects receiving at least one dose of Datscan.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The submitted studies for safety include one phase 1 study (CY95.FP.I), two phase 2 studies (CY96.FP.II & PDT02005), six phase 3 studies (PDT301, PDT304, DP008-003, PDT03007, PDT408 and Walker). For the Walker study, only spontaneously reported adverse events (AEs) were recorded and the data were not included in the pooled safety analysis.

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Table 21 shows a summary of subject diagnoses for each study included in the review of safety.

Table 21: Subjects in the safety analysis by study and diagnosis group.

Study	Parkinsonism (PD,PSP,MSA) N=409 (43%)	DLB N=168 (18%)	ET N=29 (3%)	HV N=57 (6%)	Other N=254 (27%)	Unknown N=25 (3%)	Total N=942 N, %
CY95.FP.I N %	0	0	0	12	0	0	12 (1)
CY96.FP.II	20	0	0	10	0	0	30 (3)
PDT02005	26	0	0	0	25	0	51 (5)
DP008-003	160	0	29	35	0	0	224 (24)
PDT304	142	0	0	0	37	0	179 (19)
PDT301	0	168	0	0	158	0	326 (35)
PDT408	61	0	0	0	34	25	120 (13)

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Datscan safety data were pooled across the 8 clinical studies due to the small number of subjects enrolled in the studies and the similar design of the larger, phase 3 studies. Subjects in the phase 1 and 2 studies all received a single, 3 mCi dose of Datscan by intravenous injection. Subjects enrolled in study 304 received up to 3 doses of DaTSCAN over a 3 year period. Subjects in study PDT03007 previously participated in study 003 and received two doses of study drug (1 dose in each study). Fourteen subjects in study 408 received two doses of DaTSCAN. All other subjects received a single dose of DaTSCAN.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

All patients (N=942) exposed were adults > 18 years of age who received a single administration of Datscan ranging from 3-5 mCi, which is consistent with the proposed dosage. As stated above (7.1.3), some subjects (studies 304 and 408) received up to three doses of Datscan separated by time intervals of approximately 12 months.

Table 22: Demographics of subjects in safety analysis by diagnosis.

	Parkinsonism (PD,PSP,MSA) N=409	DLB N=168	ET N=29	HV N=57	Other N=254	Unknown N=25	Total N=942
Age (yr)							
Mean	63	74	64	56	70	66	66
Min,max	35,86	54,90	46,80	32,79	25,89	31,81	25,90
Gender							
Male	61%	62%	69%	39%	55%	28%	57%
Female	39%	38%	31%	60%	45%	72%	42%
Missing	<1%			<1%			<1%
Race							
Cauc.	98%	100%	100%	93%	100%	96%	99%
Black	<1%			5%		4%	1%
Asian	1%						<1%
Other	<1%						<1%
Missing	<1%			2%			<1%

Reviewer's comments:

Demographics relating to age and gender reflect the target population. However, the safety studies were conducted in almost exclusively (99%) Caucasians. Therefore, there are little data evaluating the safety of Datscan in minority races.

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7.2.2 Explorations for Dose Response

Phase 1 and 2 studies were performed evaluating a single 3 mCi dose of Datscan administered intravenously with regards to biodistribution, clearance, and radiation dosimetry estimates. This dose was consistent with previously reported studies of ¹²³I-ioflupane performed in Finland.⁸ The final, proposed dose of 3-5 mCi was determined based upon adequate imaging results and acceptable radiation dosimetry estimates obtained in the phase 1 and 2 studies.

7.2.3 Special Animal and/or In Vitro Testing

Preclinical studies were performed to evaluate behavioral safety, cardiovascular and respiratory safety, potential Datscan interactions with therapeutic drugs for Parkinsonism, single and repeat dose toxicology, and genotoxicity of Datscan. No reproductive toxicity or carcinogenicity studies were performed, as the sponsor's request for a waiver of these studies was granted.

In conscious dogs monitored with telemetry, a study using up to 983X the maximum human dose (MHD) revealed no cardiovascular effects. There was also no treatment related effect on PQ duration, QRS interval and QTc duration at approximately 10000X the MHD, although increased blood pressure and heart rate were reported at this dose. In another dog study, Datscan (9828X MHD) induced an increased respiratory rate immediately after injection. However, no elevated respiratory rate was reported at lower doses.

In rats, behavioral changes such as hyperactivity and stereotypic behavior related to similarity in pharmacology between Datscan and cocaine were seen at very high doses, which were approximately 3000X or higher than the clinical dose of Datscan.

Datscan (0.65X – 648X MHD) was administered to male Sprague-Dawley rats and a modified Irwin-type Functional Observation Battery (FOB) conducted on the rats between 10 minutes to 8 days post dosing. There was no mortality. However, there was piloerection, labored respiration, increased defecation, touch reactivity, positional passivity, and alterations in muscle tone. The reported alteration in respiration was dose-related and treatment related, while significant alterations in muscle tone were observed at 648X MHD.

In rat models of Parkinsonism, the potential effects of Datscan on the pharmacological actions of L-DOPA, bromocriptine and amantadine were evaluated. The combination of Datscan 0.1 mg/kg and a DAT inhibitor, GBR-12935 (0.1 mg/kg), did not affect the stimulating activity of L-DOPA on locomotor activity in rats with substantia nigra bilaterally lesioned with 6-OHDA. However, combinations of Datscan (1mg/kg) and GBR-12935 (1mg/kg) did prolong the actions of L-DOPA. Furthermore, combinations of Datscan (0.1 and 1 mg/kg) and GBR-12935 (0.1 and 1 mg/kg) did not affect the

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stimulating activity of bromocriptine and amantadine on locomotor activity. Thus, Datscan did not affect the locomotor activity when administered in this experimental model of Parkinsonism in combination with L-DOPA, bromocriptine and amantadine.

Single dose and repeat-dose toxicity studies were conducted in rats, rabbits and Cynomolgus monkeys. No treatment-related mortality was reported in any of these studies. Following a single dose injection to dogs, mydriasis, increased motility, and licking were reported during administration or immediately after administration of 29480X MHD FP-CIT to dogs and a NOAEL of 1 µg/kg (98.3X MHD) was obtained. Increased heart rate, blood pressure, respiratory rate, slight decrease in motility, mydriasis and restlessness were reported in Cynomolgus monkeys administered 5880X MHD and the NOAEL in the study was 0.3 µg/kg (17.7X MHD). During single dose toxicity study, a NOAEL of 10 µg/kg (294.8X MHD) was obtained in the rats. No change in body weight or clinical pathology was reported in rabbits following a single injection of 0.06 mg/kg (3604X MHD), the only dose employed in the study.

The 14-day repeat dose toxicity studies in rats revealed stereotype behavior, increased and violent physical activity, excessive sensitivity to external stimuli, and piloerection following a daily injection of 17688X MHD. However, no treatment-related clinical signs were reported in animals administered 0.006 mg/kg/day (176.88X MHD). There were scattered blood spots in the lungs of 1/5 female in the 8844X MHD group and histopathology of the lungs showed localized mild bleeding in males in the 294.8X MHD group and in males and females injected 8844X MHD. The NOAEL in this study was 10 µg/kg/day (294.8X MHD). There were stereotype and aggressive behavior in rabbits treated with 360X and 36000X MHD for 2-weeks while increased responses to external stimuli, protruding eyes with dilated pupils, and fast or labored respiration occurred in rabbits administered 90000X MHD. No serious clinical signs were reported in Beagle dogs administered up to 9828X MHD of Datscan. However, there was mydriasis, congestion of the visible mucosa, flushing of the pinnae, reddening of the skin, or panting at this dose. The NOAEL in this study was 1 µg/kg/day (98.3X MHD).

The standard ICH battery of tests, including two *in vitro* assays covering the endpoints of gene mutation (in bacteria) and chromosomal effects (in cultured human lymphocytes and in mouse bone marrow), were evaluated. The tests were negative, indicating that FP-CIT (Datscan) demonstrates no genotoxicity potential.

7.2.4 Routine Clinical Testing

The routine clinical testing of study subjects was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

[Please see Clinical Pharmacology section (4.4.2) for further details]

There have been no human studies to investigate Datscan drug interactions. Drug interactions with Datscan are considered possible based on the mechanism of action of reversible binding to the DaT protein. Drugs which bind the DaT protein could theoretically block or reverse Datscan binding to the DaT ligand. The applicant provides a list of drugs with potential to interfere with Datscan binding (4.4.2).

Datscan use in patients with impaired excretory or metabolic function has not been evaluated because of its single dose, microgram dosing regimen. The effects of age and gender differences on Datscan pharmacokinetics have not been evaluated by the applicant.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Pharmacological effects from Datscan are not observed in humans following the intravenous administration of the proposed dose of ≤ 0.325 micrograms. Estimates from phase 2 studies indicate that Datscan occupies less than 1% of DaT proteins in the brain, with no expected pharmacological effect at this level of occupancy. The sponsor estimates that approximately 6000 vials of Datscan would have to be administered to achieve a pharmacological effect.

7.3 Major Safety Results

Tabel 23 shows a summary of adverse events for all subjects in the safety analysis.

Table 23: Adverse event summary

	Overall n (%)	Possibly DaTSCAN related * n (%)
Number of adverse events	588	73
Subjects with at least one AE	231 (25)	39 (4)
Subjects with at least one AE leading to discontinuation from the study	10 (1)	0 (0)
Subjects with at least one serious AE	36 (4)	0 (0)
Subjects with at least one AE leading to death	5 (<1)	0 (0)

**Relation to Datscan administration was determined by study investigator*

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7.3.1 Deaths

Five subjects died during the conduct of the studies. Four of the subjects were enrolled in the PDT304 study and 1 subject was enrolled in the PDT301 study. The fatal events were bronchial carcinoma (466 days after dosing), pneumonia (899 days after dosing), femoral neck fracture, myocardial ischemia and left ventricular failure (225 days after dosing), sepsis (time after dosing not available), and femoral neck fracture (366 days after dosing). None of the fatal events were considered related to DaTSCAN administration.

7.3.2 Nonfatal Serious Adverse Events

A total of 36 (4%) subjects experienced at least one serious adverse event (SAE), and no subject experienced an SAE that was considered by the investigator to be at least possibly related to Datscan administration.

7.3.3 Dropouts and/or Discontinuations

A total of 10 (1%) subjects experienced an AE that led to discontinuation from the study, and no subject experienced a possible Datscan related AE that led to discontinuation from the study.

7.3.4 Significant Adverse Events

Overall, 588 AEs were reported, with 73 (12%) of these AEs considered by the investigator to be at least possibly related to Datscan administration. A total of 231 (25%) subjects experienced at least 1 AE, and 39 (4%) subjects experienced an AE that was considered by the investigator to be at least possibly related to Datscan administration. Of the 39 subjects who experienced an AE possibly related to Datscan, the most common was headache (n=13, 1%), nausea (n=8, <1%), and vertigo, dry mouth, hunger, and dizziness (3 each, < 1%).

Table 24 summarizes the most common AEs overall, by body organ system and severity. Overall, 110 (12%) subjects experienced a mild AE, 85 (9%) subjects experienced a moderate AE, and 32 (3%) subjects experienced a severe AE. The most common AEs were related to nervous system disorders (85 subjects, 9%), followed by musculoskeletal and connective tissue disorders and gastrointestinal disorders (51 subjects each, 5%), infections (50 subjects, 5%), general disorders and administration site conditions (41 subjects, 4%), and vascular disorders (29 subjects, 3%). For all other body organ systems, the percentage of subjects with AEs was \leq 2%.

Table 24: Most common adverse events by organ system and severity.

Adverse events by system organ class	Total N (%)	Mild N (%)	Moderate N (%)	Severe/ Incapacitating N (%)	Missing N (%)
Number of subjects with at least one AE	231 (25)	110 (12)	85 (9)	32 (3)	4 (<1)
Gastrointestinal	51 (5)	28 (3)	20 (2)	3 (<1)	0 (0)
General disorders & administration site AEs	41 (4)	24 (3)	14 (1)	2 (<1)	1 (<1)
Infections/Infestations	50 (5)	32 (3)	15 (2)	3 (<1)	0 (0)
Injury, poisoning & procedural complications	21 (2)	6 (<1)	8 (<1)	7 (<1)	0 (0)
Investigations	16 (2)	13 (1)	1 (<1)	0 (0)	2 (<1)
Musculoskeletal & connective tissue disorders	51 (5)	27 (3)	21 (2)	3 (<1)	0 (0)
Nervous system	85 (9)	47 (5)	31 (3)	6 (<1)	1 (<1)
Psychiatric	16 (2)	10 (1)	5 (<1)	1 (<1)	0 (0)
Respiratory, thoracic, mediastinal disorders	22 (2)	13 (1)	8 (<1)	1 (<1)	0 (0)
Vascular disorders	29 (3)	22 (2)	7 (<1)	0 (0)	0 (0)

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Of the 39 subjects who experienced an AE possibly related to Datscan, the most common was headache (n=13, 1%), nausea (n=8, <1%), and vertigo, dry mouth, hunger, and dizziness (3 each, < 1%).

7.4.2 Laboratory Findings

There were no clinically significant mean changes from baseline for any serum biochemistry or hematology laboratory test. Urinalysis assessments including baseline and post-injection urine pH and specific gravity revealed no clinically significant changes from baseline. Analysis of shifts from baseline to post-injection for serum biochemistry,

hematology and urinalysis laboratory tests revealed increases generally matched by decreases, suggesting the changes were not related to a drug effect.

7.4.3 Vital Signs

There were no clinically significant changes in mean values from baseline to post-injection for SBP, DBP or pulse rate. Analysis of shifts from baseline to post-injection for SBP, DBP and pulse rate revealed increases generally matched by decreases, suggesting the changes were not related to a drug effect.

7.4.4 Electrocardiograms (ECGs)

Of 794 subjects with pre and post-injection EKG assessments, 446 (59%) subjects had a normal ECG tracing pre and post-baseline, and 242 (30%) subjects had an abnormal ECG tracing pre and post-injection. Thirty-eight (5%) subjects had a normal ECG tracing pre-injection and an abnormal tracing post-injection, and 48 (6%) subjects had an abnormal ECG tracing pre- and a normal tracing post-injection.

EKG interval data were only obtained in studies 301 and PDT03007. Analyses were performed comparing the baseline values, post-injection values and change from baseline values for ventricular rate, PR, QRS, RR, QT, QTc, TQcF and QTcB intervals. No clinically significant changes in mean values were observed for any of these parameters, except for the QTc (mean change from baseline of 16.5), which was obtained in only 30 patients. As seen in table 25 (next page), the results for QTcF and QTcB did not reveal any clinically significant change in mean values. .

Table 25: Electrocardiogram descriptive statistics for QT intervals.

QT interval (msec)	N	318	318	318
	Mean (SD)	402.0 (33.14)	398.6 (37.05)	-3.4 (35.04)
	Min, Max	327, 497	316, 495	-124, 108
	Median	402.0	400.0	-7.0
QTc interval (msec)	N	30	30	30
	Mean (SD)	399.8 (32.68)	416.3 (39.29)	16.5 (48.85)
	Min, Max	340, 469	340, 500	-61, 103
	Median	400.0	415.5	22.5
QTcF interval (msec)	N	318	318	318
	Mean (SD)	414.8 (25.66)	413.2 (27.64)	-1.6 (28.83)
	Min, Max	348, 497	343, 507	-88, 99
	Median	414.0	411.5	-4.0
QTcB interval (msec)	N	318	318	318
	Mean (SD)	421.4 (28.82)	420.5 (30.85)	-0.9 (33.63)
	Min, Max	348, 503	315, 520	-130, 106
	Median	419.0	418.5	-5.0

Reviewer's comment:

The overall EKG assessment results do not raise a significant safety concern for Datscan

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Findings

Not studies were performed secondary to Datscan given as a single 3-5 millicurie intravenous injection, containing less than 0.325 micrograms drug product.

7.5.2 Time Dependency for Adverse Findings

Time of onset, duration, action taken, and outcome of AEs were not analyzed in the ISS.

7.5.3 Drug-Demographic Interactions

The incidence of AEs was analyzed in the following subgroups:

- < 65 years of age and ≥65 years
- < 75 years of age and ≥75 years
- Males and females
- Race groups

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A greater percentage of subjects in the < 65 years of age group compared to the > 65 years group reported at least 1 AE, 28% vs. 22%, respectively. However, the severity and types of AEs reported in these groups are similar, and the overall differences do not appear to be clinically significant.

In the < 75 years of age group compared to the > 75 years group, a greater percentage of subjects reported at least 1 AE, 27% vs. 17%, respectively. The differences in severity and types of AEs reported in these groups do not appear to be clinically significant.

Overall, 23% of male subjects and 27% of female subjects experienced at least 1 adverse event. Again, the severity and types of AEs reported in males and females were similar and there were no clinically significant findings in this analysis.

7.5.4 Drug-Disease Interactions

An analysis of AEs by diagnosis group or any other disease-related factor was not performed.

7.5.5 Drug-Drug Interactions

No studies have been performed to investigate drug-drug interactions for Datscan.

Reviewer's comments:

Evaluation of medication effects on Datscan imaging results will be an important part of the post-marketing program. (b) (4)

Previous studies of related compounds (beta-CIT) have shown disagreement between clinical status and Datscan image results in patients receiving dopaminergic medications to treat Parkinson's disease at the time of Datscan SPECT imaging, which strengthens the concern regarding the potential effects of these medications on the performance characteristics of Datscan.^{6,10}

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No carcinogenicity study was conducted for Datscan. The sponsor requested a waiver for carcinogenicity studies and the waiver was granted.

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7.6.2 Human Reproduction and Pregnancy Data

There are no data on Datscan exposure in pregnant or lactating women including inadvertent exposure during the drug development program or in the post-marketing data. It is not known if Datscan is excreted in human milk. However, free iodine-123 is known to be excreted in human milk. Based on batch data provided by the sponsor, the level of free iodine-123 present in the final drug product is expected to be < 3%.

7.6.3 Pediatrics and Assessment of Effects on Growth

There are no data on Datscan use in pediatric subjects. The sponsor requested, and was granted a waiver for the assessment of safety and effectiveness of the product in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose:

There have been no clinical reports of overdose in patients with Datscan.

Drug Abuse Potential, Withdrawal and Rebound:

Not applicable to Datscan, which is administered as a single intravenous injection.

The mass quantity in a single administration of Datscan is < 0.325 micrograms and does not produce pharmacological effects in humans. The sponsor estimates that approximately 6000 vials of Datscan would have to be administered to achieve a pharmacological effect, which would involve administering approximately 15 liters of the other components in a Datscan vial. The sponsor states that such quantities of the product would not be available at any single time

7.7 Additional Submissions / Safety Issues

A PSUR was submitted July 7, 2009, covering the period July 28, 2008 to June 17, 2009. There were no deaths or serious reactions following the administration of Datscan in Europe. There were no non-serious reactions requiring changes to the European Datscan label.

8 Postmarket Experience

Datscan is approved for marketing in 32 countries. Estimates of patient exposure are based on number of vials shipped by the manufacturing site. Up to 7/27/2008, it is estimated that over (b) (4) patients have been exposed to Datscan. There have been no deaths reported from Datscan administration.

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Up to 7/27/2007, a total of 5 cases of severe pain on injection (4 from the same hospital) were received. One report of a serious adverse event following Datscan administration was reported. The patient was a 76 year-old man who developed an epileptic seizure 3 ½ hours after Datscan administration. The consulting neurologist attributed the epileptic seizure to hyponatremia.

Three spontaneous case reports from healthcare professionals comprising 4 non-serious unlisted reactions (epistaxis, vasovagal syncope, hypersensitivity, and sense of oppression) and one non-serious listed reaction (headache) were received during reporting for the 8th periodic safety update report (7/27/2007-7/27/2008).

9 Appendices

9.1 Literature Reviews and References

1. I.G. McKeith *et al*, Diagnosis and management of dementia with Lewy bodies, Third report of the DLB consortium. *Neurology*, 65:1863-1872, December 2005.
2. Zuzana Walker *et al*, Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *Journal of Neurology, Neurosurgery and Psychiatry*, 78:1176-1181, 2007.
3. A literature review was performed 5/29/2009 using the *Up To Date* database and the phrase "dementia with lewy bodies".
4. Andrew J. Hughes *et al*, The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service, *Brain*, 125:861-870 2002.
5. A literature review was performed 5/29/2009 using the *Up To Date* database and the phrase "Parkinson's disease".
6. An FDA neurology consult was obtained to aid in the NDA review. This consult was written by Dr. Gerald Podskalny and is available in DARRTS.
7. Gunther *et al*, [¹²⁵I]β-CIT-FE and [¹²⁵I]β-CIT-FP are superior to ¹²⁵I]β-CIT for dopamine transporter visualization: autoradiographic evaluation in the human brain. *Nuclear Medicine and Biology*, 24:629-634, 1997.
8. J.T. Kuikka *et al*, Comparison of iodine-123 labeled 2β-carbomethoxy-3β-(4-iodophenyl)tropane and 2β-carbomethoxy-3β-(4-iodophenyl)-N-(3-fluoropropyl)nortropane for imaging of the dopamine transporter in the living human brain. *European Journal of Nuclear Medicine*, 22, No. 4:356-360, April 1995.
9. Lundkvist *et al*, [O-Methyl-11C] β-CIT-FP, a potential radioligand for quantification of the dopamine transporter: Preparation, autoradiography, metabolite studies, and positron emission tomography examinations. *Nuclear Medicine Biology*, 22, No. 7:905-913, 1995.
10. Fahn *et al*, Levodopa and the progression of Parkinson's disease. *NEJM*, 351:2498-508, 2004.

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9.2 Labeling Recommendations

Please see printed label for agree-upon final version of the document.

9.3 Advisory Committee Meeting

Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee

August 11, 2009

Questions to the Committee:

1. Do the preclinical and clinical data demonstrate that DaTSCAN allows visualization of the dopamine transporter distribution within the human brain striatum? (DISCUSSION ONLY)

Committee Discussion:

Yes. The committee agreed that the data supported the contention that DaTSCAN allows visualization of the dopamine transporter distribution within the human brain striatum. One panel member suggested that a simple quantitative method may be needed to more readily interpret the findings.

2. Three phase 3 clinical studies assessed DaTSCAN images in comparison to clinical diagnoses (clinically diagnosed dementia or movement disorders). (DISCUSSION ONLY)
 - a. Is clinical diagnosis, as formed in these studies, a satisfactory diagnostic standard ("standard of truth") for the detection of abnormal dopamine transporter distribution within the human brain striatum?

Committee Discussion:

The committee did not come to a consensus regarding this question. Some of the panel members stated that clinical diagnosis is not an acceptable surrogate for a biochemical endpoint; thus, post-mortem pathology of the brain should be the standard of truth. Some panel members stated that clinical diagnosis can be a satisfactory standard of truth for Parkinson's Disease although post-mortem data is still the gold standard. A few panel members felt that this question was irrelevant since the committee is in agreement that DaTSCAN does what it purports to do and that a positive scan indicates abnormality but does not specify the disease.

- b. Does the acceptability of this standard depend on whether the clinical population had dementia or movement disorders?

Committee Discussion:

The committee was in agreement that acceptability of clinical diagnosis as a "standard of truth" does depend on whether the clinical population had dementia or movement disorders since the clinical progression of these diseases differ. Several members noted that the

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2008 discussion of amyloid imaging involved concerns that importantly differed from the DaTSCAN concerns.

3. Do the available data indicate a favorable risk to benefit profile for use of DaTSCAN as a tool to assist clinicians in the evaluation of patients with symptoms or signs suggestive of dopaminergic neurodegeneration?
 - a. If you answered, "no," discuss the types of clinical data that would be necessary to change your opinion.
 - b. If you answered, "yes," discuss whether the favorable profile applies to all patients or only specific subsets (e.g., only dementia or only movement disorders).

YES: 11 NO: 2 ABSTAIN: 1

Committee Discussion:

One panel member voted "No" because of reservations of DaTSCAN's clinical use; another member voted "No" because of safety concerns. Thus, there was no discussion of the types of clinical data that would be necessary to change their minds. The panels who voted "Yes" agreed that the favorable profile applies to all patients.

4. Discuss any considerations you regard as important for labeling or for subsequent clinical studies you believe should be performed.

Committee Discussion:

The committee recommended the following:

- *Clinical studies for use of DaTSCAN as a screening tool*
- *Clinical studies for use of DaTSCAN for diagnosis of early disease or disease progression*
- *Training standards for interpreting the scans should be developed and included in the labeling*
- *Development of a quantitative assessment of the image to provide standardization/validation of interpretation*
- *Studies to evaluate possible medication interactions*

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
----- NDA 22454	----- ORIG 1	----- GE HEALTHCARE INC	----- DA TSCAN

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHILLIP B DAVIS
08/31/2009