

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022454Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

PMR/PMC Description: The sponsor has committed to conducting 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.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/31/2011</u>
	Study/Trial Completion:	<u>04/30/2013</u>
	Final Report Submission:	<u>07/31/2013</u>
	Other:	<u>N/A</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Non-Caucasians had very limited representation within the overall NDA database. This survey-type proposal is based, in large part, upon feasibility considerations due to reports of a lower prevalence of Parkinsonian symptoms among non-Caucasians.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Title: A Retrospective Clinical Study to Compare the Rates of Agreement Between Clinical Diagnosis and Visual Assessment of DaTSCAN Images in non-Caucasian and Caucasian Patients with Parkinson's Disease or Essential Tremor.
This retrospective study will collect existing DaTSCAN (Ioflupane I 123) images and clinical diagnoses in non-Caucasians and will determine rates of agreement between a blinded visual interpretation of each subject's images and the corresponding clinical diagnosis. The rates of agreement will then be compared to the rates of agreement for Caucasians.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety

- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs? **Yes**
- Are the objectives clear from the description of the PMR/PMC? **Yes**
- Has the applicant adequately justified the choice of schedule milestone dates? **Yes**
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process? **Yes**

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

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/s/

RENE C TYSON
01/14/2011

IRA P KREFTING
01/14/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology

Application Number: NDA 22-454

Name of Drug: DaTscan (I 123 Ioflupane) Injection

Applicant: GE Healthcare

Date: January 5, 2011

Material Reviewed:

Submission Date: November 16, 2010

Receipt Date: November 17, 2010

Submission Date of Structure Product Labeling (SPL): November 16, 2010

Type of Labeling Reviewed: Word/SPL

Background and Summary

Draft labeling was sent to the Applicant on December 15, 2009 by FDA and contained a number of requested revisions detailed in the annotated draft label including a section on Drug Abuse and Dependence, citing the product as being covered under the Controlled Substances Act. GE HealthCare responded on December 17, 2009. That labeling did not include language noting that the product was covered by the Controlled Substances Act. GE accepted all of the requested changes except the text which referred to designating the product as a controlled substance.

All of the requested revisions to the label were accepted by GE except the following:

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance

9.0 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Ioflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act.

Because GE HealthCare did not accept the labeling changes as proposed by FDA, a Complete Response letter was issued on December 23, 2010.

This is a resubmission of labeling in response to the Complete Response letter issued by the Division on December 23, 2009.

The resubmitted label contained the changes requested by FDA in their December 15, 2009 correspondence and the Complete Response letter. In addition to submitting a label that contained the text requested by FDA, GE added additional text. Here is the text submitted by GE on November 16, 2010.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Ioflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act.

(b) (4)

Review

The label from GE's December 17, 2009 submission was compared to GE's resubmitted label of November 16, 2010. It incorporated the changes requested by FDA noted in the Complete Response letter of December 23, 2010. The resubmitted label was referred to the Controlled Substances Staff (CSS) for review. They recommended that the following statement be removed from the label:

(b) (4)

The CSS recommended that the following language replace the sentence above proposed by GE.

A DEA license is required for handling or administering this controlled substance.

This language was proposed to GE by FDA and GE accepted it.

The container and carton label were reviewed by the chemist and DMEPA. Both found the carton and container labels acceptable. DMEPA reviewed the proprietary name again and found it acceptable. GE was asked to relocate the NDC number on the carton and container labels to the principle display panel in accordance with 21 CFR 207.35(b)(3)(1). This was also communicated to GE and GE found it acceptable.

Recommendations

The changes requested by FDA in the resubmitted label have all been communicated to GE and found to be acceptable by them. Because there are no outstanding labeling issues and all disciplines have found the package insert and the container and carton label changes acceptable, I recommend that FDA issue an approval letter for the application.

James Moore, PharmD., M A.
Regulatory Project Manager, DMIP

Supervisory Concurrence

Kyong Kang, PharmD.
Chief, Project Management Staff
January 5, 2011

CSO LABELING REVIEW

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/s/

JAMES W MOORE
01/10/2011

KYONG A KANG
01/12/2011

Medical Officer's Consultative Review Memorandum

Submission type: Consult from Division of Drug Marketing, Advertising, and Communications (DDMAC)
Consult topic: Proposed DaTscan patient brochure
Product: DaTscan (ioflupane I 123)
Product Sponsor: GE Healthcare
NDA No. 22454
NDA Submission Date: 3/6/2009
Application status: Complete response letter sent 12/23/2009
Consult Date: 5/18/2010
Desired Completion Date: 6/21/2010
Materials Reviewed: Proposed patient brochure

Consult requested by: Carrie Newcomer, PharmD, DDMAC

Consultant: Phillip Davis, MD, Division of Medical Imaging Products (DMIP)

Through: Louis Marzella, MD, PhD, DMIP

I. Executive Summary:

Overall, the reviewer finds the content in the proposed patient brochure accurate and fact based. In the reviewer's opinion, the majority of the content is acceptable and appropriate for the intended audience. There is one exception to this opinion, which is detailed at the end of section III under "Additional Consultant Comments".

II. Background:

Drug Product:

Datscan is a radiopharmaceutical containing Iodine-123 labeled Ioflupane (ioflupane I 123), a radioisotope-labeled cocaine analog, which binds to the dopaminergic transporter (DaT) protein in the brain. The Datscan final drug product contains ¹²³I-ioflupane (< 0.325 µg active drug product), ioflupane, ethanol and sodium acetate (b) (4). DaTscan is delivered as a sterile solution in 2.5 ml vials ready for intravenous injection.

Indication:

The proposed indication for DaTscan is "for visualization of the dopamine transporter (DaT) distribution within the striatum by SPECT imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration".

Review Status:

The DaTscan NDA was received 3/9/2009, with a priority review PDUFA goal date of 9/9/2009. Following a complete review of the NDA, DMIP sent a complete response letter to the sponsor on 9/8/2009, listing multiple clinical deficiencies. The sponsor responded to these deficiencies with a submission dated 10/26/2009. DMIP's review of these responses found most responses to be acceptable. However, due to some

outstanding labeling and post-marketing study issues, including the controlled substance status of the product, an additional complete response letter was issued on 12/23/2009.



Description of consultation request:

DDMAC is reviewing a proposed patient brochure for the anticipated marketing of DaTscan, and has two questions for DMIP regarding the content of the brochure. The focus of this review, as requested, is to answer questions from DDMAC regarding content of the sponsor's proposed patient brochure.

III. Consult Questions:

(Please note sponsor claims are presented in italics):

1. The patient brochure presents the following claim:

- *“DaTscan is for adult patients who may have signs or symptoms of Parkinsonian syndromes, such as shaking or stiffness.”*

The sponsor references the Indications and Usage section of the draft PI for this claim. According to the draft PI, “. . . *DaTscan may be used to help differentiate essential tremor from tremor due to PS . . .*” Do you believe the claim in the patient brochure is accurate or should it be revised to be consistent with the Indications and Usage section of the PI?

Consultant's response:

The above claim in the patient brochure accurately describes the symptoms of a Parkinsonian syndrome in simple language. This claim is appropriate for the intended audience and does not raise concern for the reviewer.

2. The patient brochure presents the following claim:

- *“The DaTscan test will be performed in the nuclear medicine department of a hospital or in an outpatient office.”*

There are no references provided to support this claim. Do you believe this claim is accurate?

Consultant's response:

The above claim is accurate. The DaTscan SPECT procedure will be performed in the nuclear medicine department of a hospital or in an outpatient office equipped and licensed to perform nuclear medicine SPECT imaging procedures.

Additional Consultant comments:

On page 4 of the patient brochure, under the section titled “What is DaTscan?”, the first sentence of the third paragraph states “There are different types of Parkinsonian syndromes (b) (4) The most common syndrome is Parkinson’s disease, also known as PD. Other types include multiple system atrophy and progressive supranuclear palsy.” This statement might be misleading to the patient and could be clarified with additional context. Please note DaTscan cannot diagnose or differentiate between PD, multiple system atrophy and progressive supranuclear palsy (all are Parkinsonian syndromes). DaTscan SPECT visualizes the DaT protein distribution in the striatum, which may help differentiate between a Parkinsonian syndrome (PD, multiple system atrophy and progressive supranuclear palsy all included) and essential tremor (a non-Parkinsonian syndrome).

Reviewed by:

Phillip Davis, MD
Medical Officer

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
06/15/2010

LIBERO L MARZELLA
06/15/2010

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: December 11, 2009

To: Rafel Rieves, M.D., Division Director
Division of Medical Imaging and Hematology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

Silvia Calderon, Ph.D., Pharmacology Team Leader
Controlled Substance Staff (CSS)

From: Chad J. Reissig, Ph.D., Pharmacologist
Controlled Substance Staff (CSS)

Subject: Consult on NDA 22-454 for DaTSCAN
Sponsor: GE HealthCare

Background

The product that is the subject of this NDA submitted by GE HealthCare is a radiopharmaceutical that will be used to evaluate loss of nigrostriatal dopaminergic neurons in the brain. The active pharmaceutical ingredient (API) of the product is a derivative of (b) (4) cocaine. The API is clearly similar in chemical structure to cocaine (b) (4). CSS has reviewed the product labeling and recommends the following:

- 1) The drug's status as a controlled substance must be clearly marked on the outside of the product packaging. The CII symbol must appear after the commercial name.
- 2) Under the HIGHLIGHTS OF PRESCRIBING INFORMATION, The second paragraph should read:

DaTscan (Ioflupane I 123 Injection) for Intravenous Use, CII
Initial U.S. Approval: 2009
- 3) Section 9, DRUG ABUSE AND DEPENDENCE needs to be added. This section should contain the following language: "Ioflupane I 123 Injection is a Schedule II controlled substance under the Controlled Substances Act."

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

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/s/

CHAD REISSIG
12/11/2009

SILVIA N CALDERON
12/11/2009

MICHAEL KLEIN
12/14/2009

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: November 10, 2009

To: James Moore, Regulatory Project Manager
Division of Medical Imaging and Hematology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Corinne P. Moody, Science Policy Analyst
Controlled Substance Staff (CSS)

Subject: Consult on NDA 22-454 for DaTSCAN
Sponsor: GE HealthCare

Cc: Silvia Calderon, Ph.D., Pharmacology Team Leader, CSS
Chad Reissig, Ph.D., Pharmacologist, CSS

Background

The product that is the subject of this NDA submitted by GE HealthCare is a radiopharmaceutical that will be used to evaluate loss of nigrostriatal dopaminergic neurons in the brain. The active pharmaceutical ingredient (API) of the product is a (b) (4) derivative of cocaine. The API is clearly similar in chemical structure to cocaine (b) (4). The chemistry information in the NDA was unclear regarding the source and origin of the API. The sponsor must submit information that clearly states if the product does originate from cocaine (b) (4).

All of the above was submitted to the Division in a memo dated September 4, 2009. Subsequently, the Division and CSS held a teleconference on September 29, 2009 to discuss the CSS response to the Division's consult request. The Division clarified that their intention was to consult 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.

Conclusion

The active pharmaceutical ingredient (API) of the product is a derivative ^{(b) (4)} of cocaine.

In addition, all chemical intermediaries in the chemical synthetic process from the coca leaf, to the final chemical (API) are, by definition, derivatives of ^{(b) (4)} cocaine.

The Sponsor should discuss the CSA control status of DaTSCAN with the Drug Enforcement Administration (DEA). The Sponsor should ascertain whether the DEA will consider whether their product and other chemical intermediaries are eligible to be exempted from CSA controls, as the API is a prescription drug product.

However, it should be noted that the manufacturing process has to be under DEA regulations and control. The DaTSCAN product may be regulated as a narcotic and this is a DEA determination. The Sponsor needs to explain with justification why, in their opinion, DEA should not consider DaTSCAN and its chemical intermediaries, narcotics in Schedule II.

Attached are specific regulations we are relying on for this disposition. CSS has determined that if the API is derived from cocaine ^{(b) (4)}, it is by definition a Schedule II narcotic substance in the Controlled Substances Act.



Finally, the Sponsor should be aware that the current Schedule II status of DaTSCAN does not prevent its approval and marketing.

Code of Federal Regulations

§ 1310.13 Exemption of chemical mixtures; application.

(a) The Administrator may, by publication of a Final Rule in the Federal Register, exempt from the application of all or any part of the Act a chemical mixture consisting of two or more chemical components, at least one of which is not a List I or List II chemical, if:

(1) The mixture is formulated in such a way that it cannot be easily used in the illicit production of a controlled substance; and

(2) The listed chemical or chemicals contained in the chemical mixture cannot be readily recovered.

(b) Any manufacturer seeking an exemption for a chemical mixture, not exempt under § 1310.12, from the application of all or any part of the Act, may apply to the Administrator, Drug Enforcement Administration, Department of Justice, Washington, DC 20537.

(c) An application for exemption under this section shall contain the following information:

(1) The name, address, and registration number, if any, of the applicant;

(2) The date of the application;

(3) The exact trade name(s) of the applicant's chemical mixture and:

(i) If the applicant formulates or manufactures the chemical mixture for other entities, the exact trade names of the chemical mixtures and the names of the entities for which the chemical mixtures were prepared; and

(ii) If a group of mixtures (e.g. formulations having identical function and containing the same listed chemical(s)), the information required in paragraph (c)(3)(i) of this section and a brief narrative of their use.

(4) (i) The complete qualitative and quantitative composition of the chemical mixture (including all listed and all non-listed chemicals); or

(ii) If a group of mixtures, the concentration range for the listed chemical and a listing of all non-listed chemicals with respective concentration ranges.

(5) (i) The chemical and physical properties of the mixture and how they differ from the properties of the listed chemical or chemicals; and

(ii) If a group of mixtures, how the group's properties differ from the properties of the listed chemical.

(6) A statement that the applicant believes justifies an exemption for the chemical mixture or group of mixtures. The statement must explain how the chemical mixture(s) meets the exemption criteria set forth in paragraph (a) of this section.

(7) A statement that the applicant accepts the right of the Administrator to terminate exemption from regulation for the chemical mixture(s) granted exemption under this section.

(8) The identification of any information on the application that is considered by the applicant to be a trade secret or confidential and entitled to protection under U.S. laws restricting the public disclosure of such information.

(d) The Administrator may require the applicant to submit such additional documents or written statements of fact relevant to the application that he deems necessary for determining if the application should be granted.

(e) Within 30 days after the receipt of an application for an exemption under this section, the Administrator will notify the applicant of acceptance or rejection of the application. If the application is not accepted, an explanation will be provided. The Administrator is not required to accept an application if any information required pursuant to paragraph (c) of this section or requested pursuant to paragraph (d) of this section is lacking or not readily understood. The applicant may, however, amend the application to meet the requirements of paragraphs (c) and (d) of this section. If the exemption is granted, the applicant shall be notified in writing and the Administrator shall issue, and publish in the Federal Register, an order on the application. This order shall specify the date on which it shall take effect. The Administrator shall permit any interested person to file written comments on or objections to the order. If any comments or objections raise significant issues regarding any findings of fact or conclusions of law upon which the order is based, the Administrator may suspend the effectiveness of the order until he has reconsidered the application in light of the comments and objections filed. Thereafter, the Administrator shall reinstate, terminate, or amend the original order as deemed appropriate.

(f) The Administrator may, at any time, terminate or modify an exemption for any product pursuant to paragraph (e) of this section. In terminating or modifying an exemption, the Administrator shall issue, and publish in the Federal Register, notification of the removal of an exempt product or group of exempt products for which evidence of diversion has been found. This order shall specify the date on which the termination of exemption shall take effect. The Administrator shall

permit any interested party to file written comments on or objections to the order within 60 days of the date of publication of the order in the Federal Register. If any such comments or objections raise significant issues regarding any finding of fact or conclusion of law upon which the order is based, the Administrator may suspend the effectiveness of the order until he has reconsidered the order in light of comments and objections filed. Thereafter, the Administrator shall reinstate, terminate, or amend the original order as determined appropriate.

(g) A manufacturer of an exempted chemical mixture shall notify DEA in writing, of any change in the quantitative or qualitative composition of a chemical mixture that has been granted an exemption by application. Changes include those greater than the range of concentration given in the application or that remove non-listed chemical(s) given in the application as part of the formulation. A new application will be required only if reformulation results in a new product having a different commercial application or can no longer be defined as part of a group of exempted chemicals. DEA must be notified of reformulation at least 30 days in advance of marketing the reformulated mixture. For a change in name or other designation, code, or any identifier, a written notification is required. DEA must be notified of any changes at least 60 days in advance of the effective date for the change.

(h) Each manufacturer seeking exemption must apply for such an exemption. A formulation granted exemption by publication in the Federal Register will not be exempted for all manufacturers.

(i) The following chemical mixtures, in the form and quantity listed in the application submitted (indicated as the "date") are designated as exempt chemical mixtures for the purposes set forth in this section and are exempted by the Administrator from application of sections 302, 303, 310, 1007, and 1008 of the Act ([21 U.S.C. 822](#), [823](#), [830](#), [957](#) and [958](#)):

Exempt Chemical Mixtures

Manufacturer	Product name \1\	Form	Date
[RESERVED]			

\1\ Designate product line if a group.

[68 FR 23204, May 1, 2003]

Code of Federal Regulations

EXEMPTED PRESCRIPTION PRODUCTS

Section 1308.31 Application for exemption of a nonnarcotic prescription product.

(a) Any person seeking to have any compound, mixture, or preparation containing any nonnarcotic controlled substance listed in [Sec. 1308.12\(e\)](#), or in Sec. 1308.13 [\(b\)](#) or [\(c\)](#), or in [Sec. 1308.14](#), or in [Sec. 1308.15](#), exempted from application of all or any part of the Act pursuant to section 201(g)(3)(A), of the Act ([21 U.S.C. 811\(g\)\(3\)\(A\)](#)) may apply to the Administrator, Drug Enforcement Administration, Washington, DC 20537, for such exemption.

(b) An application for an exemption under this section shall contain the following information:

- (1) The complete quantitative composition of the dosage form.
- (2) Description of the unit dosage form together with complete labeling.
- (3) A summary of the pharmacology of the product including animal investigations and clinical evaluations and studies, with emphasis on the psychic and/or physiological dependence liability (this must be done for each of the active ingredients separately and for the combination product).
- (4) Details of synergisms and antagonisms among ingredients.
- (5) Deterrent effects of the noncontrolled ingredients.
- (6) Complete copies of all literature in support of claims.
- (7) Reported instances of abuse.
- (8) Reported and anticipated adverse effects.
- (9) Number of dosage units produced for the past 2 years.

(c) Within a reasonable period of time after the receipt of an application for an exemption under this section, the Administrator shall notify the applicant of his acceptance or non-acceptance of the application, and if not accepted, the reason therefor. The Administrator need not accept an application for filing if any of the requirements prescribed in [paragraph \(b\)](#) of this section is lacking or is not set forth so as to be readily understood. If the applicant desires, he may amend the application to meet the requirements of [paragraph \(b\)](#) of this section. If accepted for filing, the Administrator shall publish in the Federal Register general notice of this proposed rulemaking in granting or denying the application. Such notice shall include a reference to the legal authority under which the rule is proposed, a statement of the proposed rule granting or denying an exemption, and, in the discretion of the Administrator, a summary of the subjects and issues involved.

The Administrator shall permit any interested person to file written comments on or objections to the proposal and shall designate in the notice of proposed rule making the time during which such filings may be made. After consideration of the application and any comments on or objections to his proposed rulemaking, the Administrator shall issue and publish in the Federal Register his final order on the application, which shall set forth the findings of fact and conclusions of law upon which the order is based. This order shall specify the date on which it shall take effect, which shall not be less than 30 days from the date of publication in the Federal Register unless the Administrator finds that conditions of public health or safety necessitate an earlier effective date, in which event the Administrator shall specify in the order his findings as to such conditions.

(d) The Administrator may revoke any exemption granted pursuant to section 201(g)(3)(A) of the Act ([21 U.S.C. 811\(g\)\(3\)\(A\)](#)) by following the procedures set forth in [paragraph \(c\)](#) of this section for handling an application for an exemption which has been accepted for filing.

[38 FR 8254, Mar. 30, 1973. Redesignated at 38 FR 26609, Sept. 24, 1973, as amended at 44 FR 18968, Mar. 30, 1979; 52 FR 9803, Mar. 27, 1987]

Code of Federal Regulations

Section 1308.32 Exempted prescription products.

The compounds, mixtures, or preparations that contain a nonnarcotic controlled substance listed in [Sec. 1308.12\(e\)](#) or in Sec. 1308.13 [\(b\)](#) or [\(c\)](#) or in [Sec. 1308.14](#) or in [Sec. 1308.15](#) listed in the Table of Exempted Prescription Products have been exempted by the Administrator from the application of sections 302 through 305, 307 through 309, 1002 through 1004 of the Act (21 U.S.C. [822-825](#), [827-829](#), and [952-954](#)) and Secs. [1301.13](#), [1301.22](#), and Secs. [1301.71](#) through [1301.76](#) of this chapter for administrative purposes only. An exception to the above is that those products containing butalbital shall not be exempt from the requirement of 21 U.S.C. [952-954](#) concerning importation, exportation, transshipment and in-transit shipment of controlled substances. Any deviation from the quantitative composition of any of the listed drugs shall require a petition of exemption in order for the product to be exempted. A listing of the Exempted Prescription Products may be obtained by submitting a written request to the Drug and Chemical Evaluation Section, Drug Enforcement Administration, Washington, DC 20537.

[62 FR 13967, Mar. 24, 1997]

Code of Federal Regulations

Section 1300.01 Definitions relating to controlled substances.

(a) Any term not defined in this part shall have the definition set forth in section 102 of the Act ([21 U.S.C. 802](#)), except that certain terms used in part [1316](#) of this chapter are defined at the beginning of each subpart of that part.

(b) As used in parts [1301](#) through [1308](#) and part [1312](#) of this chapter, the following terms shall have the meanings specified:

(30) The term narcotic drug means any of the following whether produced directly or indirectly by extraction from substances of vegetable origin or independently by means of chemical synthesis or by a combination of extraction and chemical synthesis:

(i) Opium, opiates, derivatives of opium and opiates, including their isomers, esters, ethers, salts, and salts of isomers, esters, and ethers whenever the existence of such isomers, esters, ethers and salts is possible within the specific chemical designation. Such term does not include the isoquinoline alkaloids of opium.

(ii) Poppy straw and concentrate of poppy straw.

(iii) Coca leaves, except coca leaves and extracts of coca leaves from which cocaine, ecgonine and derivatives of ecgonine or their salts have been removed.

(iv) Cocaine, its salts, optical and geometric isomers, and salts of isomers.

(v) Ecgonine, its derivatives, their salts, isomers and salts of isomers.

(vi) Any compound, mixture, or preparation which contains any quantity of any of the substances referred to in paragraphs (b)(31)(i) through (v) of this section.

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

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/s/

CORINNE P MOODY
11/10/2009

MICHAEL KLEIN
11/10/2009

MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 4, 2009

To: James Moore, Regulatory Project Manager
Division of Medical Imaging and Hematology Products

Through: Michael Klein, Ph.D., Director
Controlled Substance Staff (CSS)

From: Corinne P. Moody, Science Policy Analyst
Controlled Substance Staff (CSS)

Subject: Consult on NDA 22-454 for DaTSCAN
Sponsor: GE HealthCare

Background

The product that is the subject of this NDA submitted by GE HealthCare is a radiopharmaceutical that will be used to evaluate loss of nigrostriatal dopaminergic neurons in the brain. The active pharmaceutical ingredient (API) of the product may be a derivative [REDACTED] (b) (4) of cocaine. The API is clearly similar in chemical structure to cocaine [REDACTED] (b) (4). The chemistry information in the NDA is unclear regarding the source, so CSS is unable to make that determination. The sponsor should submit information that clearly states if the product does originate from cocaine [REDACTED] (b) (4)

Please note the following citation from the Controlled Substances Act:

21 § 812 Schedules of controlled substances Schedule II (a) Unless specifically excepted or unless listed in another schedule, any of the following substances whether produced directly or indirectly by extraction from substances of vegetable origin, or independently by means of chemical synthesis, or by a combination of extraction and chemical synthesis: (4)Coca leaves except coca leaves and extracts of coca leaves from which cocaine, ecgonine, and derivatives of ecgonine or their salts have been removed; cocaine, its salts, optical and geometric isomers, and salts of isomers; ecgonine, its derivatives, their salts, isomers, and salts of isomers; or any compound, mixture, or preparation which contains any quantity of any of the substances referred to in this paragraph.

Conclusion

CSS has determined that if the API is derived from cocaine (b) (4) it is by definition a Schedule II narcotic substance in the Controlled Substances Act. The sponsor may contact the Drug Enforcement Administration for further assistance regarding the control status of this product.

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

/s/

CORINNE P MOODY
09/04/2009

MICHAEL KLEIN
09/04/2009

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-454 Supplement # Efficacy Supplement Type SE-

Proprietary Name: DataSCAN
Established Name: Ioflupane I-123
Strengths:

Applicant: GE Health Care
Agent for Applicant (if applicable):

Date of Application: March 6, 2009
Date of Receipt: March 9, 2009
Date clock started after UN:
Date of Filing Meeting: April 22, 2009
Filing Date: May 8, 2009
Action Goal Date (optional):

User Fee Goal Date: September 9, 2009

Indication(s) requested: 1

Type of Original NDA: (b)(1) (b)(2)
AND (if applicable)
Type of Supplement: (b)(1) (b)(2)

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES
This application is: All electronic Combined paper + eNDA
This application is in: NDA format CTD format
Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES x NO
- Exclusivity requested? YES, 5 Years NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
- Correctly worded Debarment Certification included with authorized signature? YES x NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.
NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., “[Name of applicant] hereby certifies 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.” Applicant may not use wording such as “To the best of my knowledge”
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES x NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES x NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO x
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES x NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section) YES x NO
- PDUFA and Action Goal dates correct in tracking system? YES x NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers:
- Are the trade, established/proper, and applicant names correct in COMIS? YES x NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO x
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) January 31, 2008 NO
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO x
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES x NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES x NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES x NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES x NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A x YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES x NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES x NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES NO x

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES x NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES x NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES x NO
- If a parenteral product, consulted to Microbiology Team? YES x NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 7, 2009

NDA #: 22-454

DRUG NAMES: DaTSCAN

APPLICANT: GE HealthCare

BACKGROUND: This is a radiopharmaceutical that has been designated as a priority application for review. It is indicated to visualization of the dopamine transporter (DAT) within the striatum by single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of patients presenting with symptoms or signs suggestive of Parkinsonian syndrome. Datscan is not indication for monitoring disease progression or response to therapy. I is a new molecular entity.

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Rafel Rieves, Libero Marzealla, Phillip Davis, Jyoti Zalkikar, Mark Levenson, Sunday Awe, Adebayo Lanionu, Christy John, Young Moon Choi, Ravindra Kasliwal, Eldon Leutzinger,

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization

Reviewer

Medical:	Phillip Davis
Secondary Medical:	Libero Marzella
Statistical:	Mark Levenson
Pharmacology:	Sunday Awe
Statistical Pharmacology:	
Chemistry:	Ravindra Kasliwal
Environmental Assessment (if needed):	
Biopharmaceutical:	Christy John
Microbiology, sterility:	Bryan Riley
Microbiology, clinical (for antimicrobial products only):	
DSI:	Lauren Iacono-Connors
OPS:	
Regulatory Project Management:	James Moore
Other Consults:	Gerald Podskalny

Per reviewers, are all parts in English or English translation? YES NO
If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known 8/11/09

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed?
YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. Convey document filing issues/no filing issues to applicant by Day 74.

Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO

If “Yes,” to (c), proceed to question 7.

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES NO

If “No,” skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO

11. Is the application for a duplicate of a listed drug whose only difference is YES NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

JAMES W MOORE

09/03/2009

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology

Application Number: NDA 22-454

Name of Drug: Datscan (I 123 Ioflupane) Injection

Applicant: GE Healthcare.

Material Reviewed:

Submission Date: March 6, 2009

Receipt Date: March 9, 2009

Submission Date of Structure Product Labeling (SPL): March 9, 2009

Type of Labeling Reviewed: Word/SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies were identified in the proposed labeling.

- (1) Add the "September 2009" to the label adjacent to "Initial U.S. Approval:" and remove "XXXX" in the highlights section of the label.
- (2) Remove the date adjacent to "revised" in the highlights section of the label.

Recommendations

The requested changes were noted in the draft labeling and was sent to GE Healthcare on Monday, September 1, 2009. The Division has requested that the labeling be returned to FDA as soon as possible.

James Moore, PharmD., M.A.
Project Manager, DMIHP

Supervisory Comment/Concurrence:

Kyong Kang, PharmD.
Chief, Project Management Staff
September 3, 2009

Drafted: JM/August 26, 2009

Revised/Initialed:KK/JM/September 3, 2009

Finalized: JM/September 3, 2009

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

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

/s/

JAMES W MOORE
09/03/2009

KYONG A KANG
09/03/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 12, 2009

TO: James Moore, Regulatory Project Manager
Phillip Davis, Medical Officer
Division of Medical Imaging and Hematology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA 22-454

APPLICANT: GE Healthcare

DRUG: DaTSCAN® (I¹²³) (Ioflupane)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: DaTSCAN is a radiopharmaceutical containing [I¹²³] 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.

CONSULTATION REQUEST DATE: 05/28/2009

DIVISION ACTION GOAL DATE: 09/08/2009

PDUFA DATE: 09/09/2009

I. BACKGROUND:

DaTSCAN is a radiopharmaceutical containing I¹²³, ioflupane, a cocaine analog, which binds to the dopamine transporter protein (DaT) found in the axon terminals (located in striatum) of pre-synaptic nigrostriatal neurons in the brain. Imaging DaTSCAN binding to DaT proteins in the brain by single photon emission computed tomography (SPECT) is 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 age-related loss of nigrostriatal neurons. DaTSCAN is administered by intravenous injection with a proposed dose of 5 millicuries, which contains approximately 0.3 micrograms of ioflupane.

GE Healthcare seeks approval of DaTSCAN for detecting loss of functional nigrostriatal dopaminergic neurons by SPECT imaging in patients presenting with symptoms or signs suggestive of dopaminergic neurodegeneration in this NDA 22454.

Two clinical sites were inspected; that of Dr. Clive Holmes, Site number 23, for his conduct of phase III study PDT301, and that of Professor Alessandro Padovani, Site number 26, for his conduct of phase III study PDT301. These sites were selected for inspection because they are considered most important in demonstrating efficacy and safety claims made by the applicant. In addition, Site 23 [REDACTED] (b) (4) and Site 26 was selected because it enrolled more patients than any other site for study PDT301.

For Studies DPT301 and DPT304, independent DaTSCAN SPECT image assessment was conducted in collaboration with the Clinical Research Organization ([REDACTED] (b) (4) under protocol; Blinded Image Evaluation (BIE) PDT 301 and BIE SPECT Evaluation Protocol PDT304. Therefore, [REDACTED] (b) (4) was inspected for their conduct of independent image analyses.

Protocol: PDT301 “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.”

Blinded Image Evaluation Protocol: PDT301: "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."

Blinded Image Evaluation SPECT Evaluation Protocol: PDT304: “An Open Label, Phase 3, Clinical Study to Assess the Striatal Uptake of an Intravenous Solution Containing the Dopamine Transporter Radio-ligand, DaTSCAN, in Patients with Early Parkinsonism.”

II. RESULTS (by Site):

Name of CI, IRB, or Sponsor Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Dr. Clive Holmes Southampton Memory Assessment & Research Center, Moorgreen Hospital, Botley West End, Southampton, Hampshire, S030 3JB, UK	Protocol PDT301/18 subjects	July 20-23, 2009	Pending Interim classification: NAI
CI #2: Dr. Alessandro Padovani Neurologia 2 Spedali Civili di Brescia Piazzale Ospedale, 1 I-25123 Brescia, Italy	Protocol PDT301/29 subjects	July 28-31, 2009	Pending Interim classification: NAI
(b) (4)	BIE Protocol PDT301/235 subjects evaluable for efficacy BIE SPECT Evaluation Protocol PDT304/102 subjects evaluable for efficacy	July 13-17, 2009	Pending Interim Classification VAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. CI#1: Dr. Clive Holmes

Southampton Memory Assessment & Research Center
Moorgreen Hospital
Botley West End
Southampton, Hampshire
S030 3JB, UK

- a. What was inspected:** The study records of all 18 subjects enrolled into study Protocol PDT301, and under the care of Dr. Holmes, were audited in accordance with the clinical investigator compliance program, CP 7348.811. Seventeen subjects received test article and 16 completed the 12 month follow-up. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms for all enrolled subjects.

The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** The investigator was found to be adequate in the execution of the Protocol PDT301. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Briefly, Subject 010 was included in the study in error. Prior to this subject receiving any test article, the site found that Subject 010 did not meet the inclusion/exclusion criteria based on CT brain scan results. Subject 009 did not complete the 12 month follow-up apparently due to loss of interest in completing the study.

The investigation also revealed that at this site it appears that it is acceptable for the physicians to determine thyroid blocking time based on their current clinical practices. The protocol PDT301, Section 10.3, states that, “subjects must undergo appropriate thyroid blocking treatment prior to injection to minimize thyroid uptake of radioactive iodine, for example by oral administration of 120 mg of potassium iodide 1-4 hours prior to injection...” This site administered blocking agent, in this case potassium iodate, with times of administration from 12 to 40 minutes prior to injection. According to the field investigator, when questioned, the medical monitor informed that she also noticed this deviation from protocol recommendations and notified the sponsor. Since the protocol only provided a recommendation on how a site might block the thyroid from test article uptake, the sponsor permitted this investigator to continue the practice as described above. Since the protocol is not definitive on which methods may be employed by the sites for blocking the thyroid prior to injection of test article the review division may wish to consider the impact of this practice on subjects treated under study PDT301 at this site on relevant study endpoints.

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. SAEs were properly documented and reported. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Holmes’ site, associated with study PDT301 submitted to the Agency in support of NDA 22-454, appear reliable based on available information. The general observations and actions on inspection are based on preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: Dr. Alessandro Padovani

Neurologia 2
Spedali Civili di Brescia
Piazzale Ospedale, 1
I-25123 Brescia, Italy

- a. What was inspected:** The study records of all 29 subjects enrolled into study Protocol PDT301, and under the care of Dr. Padovani, were audited in accordance with the clinical investigator compliance program, CP 7348.811. Twenty five subjects received test article and 23 completed the 12 month follow-up. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent forms for all enrolled subjects.

The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** The investigator was found to be adequate in the execution of the Protocol PDT301. The study was found to be well controlled and well documented. No significant regulatory deviations were observed. Briefly, there were several minor protocol deviations. The Cambridge Cognitive Examination-Revised (CAMCOG-R) test was to be administered for each subject at the baseline visit as part of a series of neuropsychiatric tests. For 8 subjects (subjects 012, 013, 018, 022, 023, 024, 025 and 028) the CAMCOG-R test scores were calculated including the response from question 156, but according to the test instructions the total score was to be calculated without counting the score assigned to the response to question 156. Also, an ECG was to be performed prior to but within 30 minutes of administration of the test article, however, for 5 subjects (subjects 004, 006, 014, 016 and 020) the ECG test was performed from >30 to ≤ 45 minutes before administration of the test article.

Consistent with the routine clinical investigator compliance program assessments the inspection focused on compliance with protocol inclusion/exclusion criteria and consistency of efficacy data found in source documents with that reported by the sponsor to the agency. CRFs were assessed for data consistency with the source documents. SAEs were properly documented and reported. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Padovani's site, associated with study PDT301 submitted to the Agency in support of NDA 22-454, appear reliable based on available information. The general observations and actions on inspection are based on

preliminary communications with the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

3.



a. What was inspected:

The CRO was inspected completing the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. Specifically, the inspection covered adherence to the blinded image evaluation protocols PDT301 and PDT304, (b) (4) Procedures, training of the blinded image readers, image data QA, the adequacy and validation of the BIE workstation, and a comparison of data contained in CRFs found at the site with the data listings submitted in NDA 22454 for the primary efficacy endpoint.

The audit confirmed that for study PDT301, there were 235 subjects evaluable for efficacy and for study PDT304, there were 102 subjects evaluable for efficacy. Inclusive dates of images evaluated for study PDT301 were from 9/14/04 to 7/25/05, and for study PDT304 were from 1/7/04 to 9/22/05.

The study records of 490 subjects enrolled into Study Protocol PDT301 and/or PDT304 were audited. Specifically, for Study PDT301, the 48 hour follow-up assessment data listing was verified for readers A, B & C for a total of 316 subjects at Sites 001-014, 016-033, 036-041, 043, 044 and 047 with 904 total data points reviewed. For Study PDT304 the baseline imaging, 18 month follow-up, and 36 month follow-up (single or in combination) assessment data listings were verified for readers A, B & C for a total of 174 subjects at sites 001-007 & site 010 with 1199 total data points reviewed.

The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

b. General observations/commentary:

Comparison of the data found in the CRF to 2103 data listings provided in the NDA 22-454 found 2 data points that did not match the CRFs for the PDT304 study. Briefly, for the randomization code A7256 (Site 001, Subject 25, 36 month follow-up), the CRF lists “abnormal type 2”, while the data listing is recorded as “normal.” For

randomization code C4692 (site 002, subject 61, 36 month follow-up), the CRF lists “abnormal type 2”, while the data listing is recorded as “abnormal type 1.” There were several instances where data audit trail quality control forms had incorrect audit trail numbers on them, however, this appears to be an artifact of the CROs in-house software and not indicative of systematic errors in audit activities.

A Form FDA 483, Inspectional Observations, was issued to the firm citing one observation.

Observation 1. The investigation was not conducted in accordance with the investigational plan.

Specifically, training records including BIE Mock Read Results and the BIE Monitor Report for the mock read, according to the Independent Reader Training and Archiving sections set forth in the Protocol PDT304, were not available for review.

- c. **Assessment of data integrity:** The data generated at this site, as it pertains to studies PDT301 and PDT304 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this CRO submitted to the agency as part and in support of NDA 22-454 and appear reliable.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on preliminary review of inspectional findings, the study data collected by Dr. Holmes and Dr. Padovani appear reliable. The inspection of the CRO (b) (4), did identify issues of concern regarding lack of training records and documentation for mock reads for Study PDT304. In addition, there were several instances where data audit trail quality control forms had incorrect audit trail numbers on them; however, this appears to be an artifact of the CROs in-house software and not indicative of systematic errors in audit activities.

The final reports (EIRs) have not been completed to date for any of these 3 inspections. Only the CRO was issued a Form FDA 483. Notwithstanding the CRO deficiencies, the data submitted to the agency in support of NDA 22-454 appear reliable. The CRO acknowledges their deficiencies and promised the FDA investigator a written response to the Form FDA 483 as well as corrective actions.

Observations noted above are based on the preliminary communications provided by the field investigator and a copy of the Form FDA 483, inspectional observations, issued to the CRO; (b) (4). An inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

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Tejashri Purohit-Sheth, M.D.
Branch Chief
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/s/

LAUREN C IACONO-CONNORS
08/12/2009

TEJASHRI S PUROHIT-SHETH
08/12/2009



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: August 11, 2009
To: Rafel Dwaine Rieves, MD, Acting Director
Division of Medical Imaging and Hematology Products
Through: Todd Bridges, RPh, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis
From: Denise V. Baugh, PharmD, BCPS, Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): DaTSCAN (Ioflupane I 123) Injection
Application Type/Number: NDA# 22-454
Applicant: GE Healthcare
OSE RCM #: 2009-842

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1 INTRODUCTION

This review is written in response to a request from the Division of Medical Imaging and Hematology Products for assessment of labels and labeling (submitted April 16, 2009) for DaTSCAN (Ioflupane I 123) Injection for their vulnerability to medication errors. The proprietary name, DaTSCAN was reviewed and found to be acceptable (OSE Review # 2009-744 dated June 29, 2009).

2 METHODS AND MATERIALS

DMEPA used Failure Mode and Effects Analysis (FMEA) in our evaluation of the container label, shield label and insert labeling submitted as part of the April 16, 2009 submission (see Appendices A and B).

3 RECOMMENDATIONS

Our evaluation noted areas where information on the container labels and shield labeling can be improved to minimize the potential for medication errors. Section 3.1, *Comments to the Applicant*, contains our recommendations for the container label and shield label. We request these recommendations be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Janet Anderson, OSE Regulatory Project manager, at 301-796-0675.

3.1 COMMENTS TO THE APPLICANT

Container Label and Shield Label

1. As stated in our July 14, 2009 correspondence granting the use of the proprietary name, DaTSCAN, we concluded that the name, 'DaTSCAN' is acceptable on the condition that the last five letters, '-TSCAN' be presented in lower case letters so it reads 'Datscan' on all labels and labeling. Presenting the '-TSCAN' portion of the name in capital letters is consistent with lettering which is typically reserved for differentiating known look-alike established name pairs or in rare circumstances for proprietary name pairs to help reduce the risk of name confusion resulting in medication error. Since 'DaTSCAN' is not a name that has been involved in name confusion, the capitalization of the letters '-TSCAN' is inappropriately applied. Therefore, revise all labels and labeling so that the '-TSCAN' portion of the name is presented in lower case letters. The name should read "Datscan" on all labels and labeling.
2. To improve readability of the proprietary name, present the first letter 'a' in the same font color as the other letters of the name.
3. Relocate the NDC number to the top third of the principal display panel of the label in accordance with 21 CFR 207.35(b)(3)(i).

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/s/

DENISE V BAUGH
08/11/2009

TODD D BRIDGES
08/11/2009

DENISE P TOYER
08/11/2009

CAROL A HOLQUIST
08/11/2009

INTRODUCTION

GE Healthcare submitted a New Drug Application, NDA 22-454 for DaTSCAN [Ioflupane I¹²³ Injection] on March 6, 2009, for the proposed indication of 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. GE Healthcare requested and FDA granted a Priority Review, because DaTSCAN may provide clinically relevant information on the dopaminergic system, not available by any other imaging method; thereby, aiding in earlier diagnosis and treatment decisions of certain movement or cognitive disorders.

Under 21 CFR 312.10, GE Healthcare requested, and FDA granted waivers for carcinogenicity and reproductive and developmental toxicity studies, as DaTSCAN is a diagnostic imaging agent intended for either single-once-in-a-lifetime administration, or for infrequent use to monitor disease progression. GE Healthcare also reports¹ that no embryonic or fetal toxicity studies, or peri- or post-natal studies were conducted as DaTSCAN is not indicated for women that are pregnant or breastfeeding.

The Division of Division of Medical Imaging and Hematology Products (DMIHP) asked the Maternal Health Team (MHT) to review the Pregnancy and Nursing Mothers section of DaTSCAN [Ioflupane I¹²³ Injection] labeling.

BACKGROUND

Pregnancy and Nursing Mothers Labeling

The Maternal Health Team (MHT) has been working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates “the spirit” of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008). The MHT reviewer ensures that the appropriate regulatory language is present and that available information is organized and presented in a clear and useful manner for healthcare practitioners. Animal data in the pregnancy subsection is presented in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human exposure or dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

Radiopharmaceutical Use in Pregnancy and Lactation

The administration of radiopharmaceuticals to a pregnant or breastfeeding woman results in the transfer and absorption of radionuclides to the embryo, fetus, or nursing child from maternal tissues, transfer across the placenta, or through breast milk.² Potential effects of radiation on the fetus depend on the fetal stage of development, the magnitude of the radiation dose. Robert Brent MD, PhD³ states that that published reported dose of radiation that results in an increased incidence of birth defects or miscarriage is above 20 rad (200 mSV). The 2008 Society of Nuclear Medicine Board Review⁴ reported that fetal radiation doses less than 5 rad (50 mGy) produces negligible effects while doses greater than 15 rad (150 mGy) have been associated with congenital anomalies.

¹ See NDA 22-454, Nonclinical Overview, p. 24

² Risica S, Fattibene F., Mazzei C., Nuccetelli C, Rogani A. Radionuclides in pregnancy and breastfeeding. *Microchemical J.* 73 (2002) 251-264

³ Brent R. Pregnancy and Radiation Exposure. <http://hps.org>. Updated May 26, 2009

⁴ See www.snm.org

Brent⁵ also reports that animal developmental toxicity studies involving the radiation of pregnant animals are important and predictive of human risks.

This review provides MHT's suggested revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of DaTSCAN [Ioflupane I¹²³ Injection] labeling. Appendix A of this review provides a tracked-changes version of labeling that highlights the recommended MHT revisions.

SUMMITTED LABELING

Sponsors Proposed Pregnancy and Nursing Mothers Labeling



MHT Comment: Language revised to approximate required regulatory language for pregnancy and nursing information in Highlights of Prescribing Information.

⁵ Brent R. Saving lives and changing family histories: appropriate counseling of pregnant women and men and women of reproductive age, concerning the risk of diagnostic radiation exposures during and before pregnancy. Am J Obstet and Gyn. 2009 Jan;200(1):4-24

MHT Comments:

- 1. We deleted the language on the unknown effect on reproductive capacity (even though it is appropriate Pregnancy Category C regulatory language) because reproductive capacity information belongs in subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. We recommend adding the unknown effect of DaTSCAN on reproductive capacity to subsection 13.1 of DaTSCAN labeling.*
- 2. We added additional clinical consideration information regarding using DaTSCAN during pregnancy.*

MHT Comment: We revised the Nursing Mothers subsection to emphasize the importance of pumping and discarding breast milk while breastfeeding is interrupted in order to maintain the mother's milk supply. In addition, we revised the time period for lactation interruption. (b) (4)

The rate of clearance of radioactivity from breast milk depends on the physical half life (radioactive half-life) of ¹²³I (13.2 hours), and the general recommendation for iodine-containing products is to resume breastfeeding 10 half-lives⁶ after administration which would be 6 days for ¹²³-I.

MHT SUMMARY AND RECOMMENDATIONS

It is critical that clinicians have adequate and optimal information available to guide them with therapeutic decision making and counseling with regard to radionuclide use in pregnant and nursing women. Adequate preclinical testing should be available before females of childbearing potential are

⁶ Stabin MG, Breitz H. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. J Nucl Med 2000; 41:863-873

exposed to these products. We acknowledge that the use of DaTSCAN in pregnant or nursing women will probably be rare because the diagnostic indications are for conditions that have very low incidence rates in women of childbearing age; however, adequate use information in pregnant and nursing women should be available for all radionuclide products to better inform labeling and clinical decision making.

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Appendix A - MHT Tracked-Changes Labeling Revisions

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/s/

Jeanine Best
6/15/2009 09:21:01 AM
LABELING REVIEWER

Karen Feibus
6/15/2009 09:34:21 AM
MEDICAL OFFICER
I agree with the content and recommendations contained in
this review

Lisa Mathis
6/17/2009 12:20:22 PM
MEDICAL OFFICER

Consultation Request

IND (Serial Number)	NDA 22-454 (0000)
Sponsor:	GE Healthcare
Drug:	DaTSCAN [Ioflupane 1123 Injection]
Proposed Indication:	Detecting loss of functional nigrostriatal dopaminergic neurons
Material Submitted:	Consult received April 28, 2009
Correspondence Date:	April 22, 2009
Date Received / Agency:	April 24, 2009
Date Review Completed	May 19, 2009
Revised	June 4, 2009
Reviewer:	Gerald D. Podskalny, D.O. Medical Reviewer, DNDP, ODE I

1. Introduction

The Division of Medical Imaging and Hematology Products (DMIHP) requested this consult from the Division of Neurology Products (DNP) regarding an investigational imaging product DaTSCAN [^{123}I] ioflupane. The sponsor for this product and NDA application is GE Healthcare. The consult instructions requested DNP to answer 3 specific questions (1, 2a, 2b). A response to question 1 regarding the sponsor's request for priority review status is considered highly time sensitive. The DNP response to the remaining two questions (2a, 2b) regarding the efficacy data, claim, and assistance with assistance with preparing for an advisory committee is needed for a later date, May 14, 2009.

Drug Product

The drug substance in DaTSCAN is [^{123}I]ioflupane. DaTSCAN is an iodine containing diagnostic radiopharmaceutical for intravenous injection. DaTSCAN is a radio-labeled, cyclotron-produced product with a physical half-life of 13.2 hours, which decays to ^{123}Te by electron capture with the emission of gamma radiation (159 keV). The product is supplied in a 10-mL glass vial closed with a rubber stopper and sealed with an aluminum cap. This diagnostic radiopharmaceutical is administered as a single I.V. injection. All of the clinical trial participants were pre-treated with iodine to block uptake by the thyroid.

Mode of Action

The intracellular target for [^{123}I]ioflupane is the dopamine transporter (DAT) protein, which functions to help the neurons terminate neuronal signaling and recycle dopamine. In vivo animal studies demonstrate specific uptake and retention of [^{123}I]ioflupane in normal striatum (mouse, rat, dog, and monkey). In Parkinsonian animal models produced by administration of toxins such as 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) [^{123}I]ioflupane uptake was reduced in the striatum in these animals demonstrating loss of functional nigrostriatal

dopaminergic neurons. In humans, the pharmacokinetics of [¹²³I]ioflupane leads to the uptake and selective retention of the iodine-123 radionuclide within dopaminergic nigrostriatal neurons in the brain. Radioactive decay of the iodine-123 to ¹²³Te emitting gamma radiation can be detected externally using gamma (3 headed) detectors, allowing visualization of the striatum through single photon emission computed tomography (SPECT) imaging.

Recommended Dose The recommended dose is 111 to 185 MBq (3 to 5 mCi).

Potential Need for Thyroid Blockade: In the proposed product label the sponsor instructs prescribers of DaTSCAN to consider blocking the patient's thyroid gland with Potassium Iodide Oral Solution (Lugol's Solution) at least 1 hour prior to receiving DaTSCAN. This consideration is emphasized in patients who may live in Iodine poor areas or have certain medical conditions affecting the thyroid.

Regulatory Status

DaTSCAN has been approved in Europe (EMEA) since 2000 however, the approved indication in the EU is much narrower than the indication requested in the U.S. application. The approved indication in Europe is:

"detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain Parkinsonian Syndromes (PS), in order to help differentiate Essential Tremor from PS related to idiopathic Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). DaTSCAN is unable to differentiate between PD, MSA and PSP. DaTSCAN also indicated to help differentiate probable DLB from Alzheimer's disease. DaTSCAN is unable to discriminate between DLB and PD dementia. "

Consult Question 1

The DMIHP requests evaluation of this application to determine whether it should be reviewed as a priority or standard application based on the following indication:

“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.”

Review of The Sponsor's Rational For Requesting Priority Review Status.

The sponsor states as part of the rational supporting their request for priority review that DaTSCAN's “Characteristic image patterns allow the facile assessment of a patient's nigrostriatal dopaminergic neuronal function as either normal or abnormal, which assists in the diagnostic work-up of patients with movement and cognitive disorders where loss of this function is suggested by clinically observed signs and symptoms”.

In the justification for priority review the sponsor states: “Since the treatment approach for dopamine-deficient disorders (primarily dopamine replacement therapy) is inappropriate when there is no dopamine deficiency, and treatment of psychotic symptoms with neuroleptics is contraindicated when there is a dopamine-deficient state, assessment of the dopaminergic system would be expected to aid determination of the correct treatment pathway for the patient”. Patients with atypical parkinsonian syndromes such as Multiple System Atrophy, Progressive Supranuclear Palsy and Dementia with Lewy Bodies may benefit symptomatically from treatment with dopaminergic medications. The claim that “treatment with dopamine replacement in patients with no (or lower deficit compared to PD) dopamine deficit is inappropriate”, is inaccurate. The sponsor’s justification ignores potential limits of this technology that includes problem of potential down regulation of DAT caused medication used to treat the symptoms of PD. Patients exposed to levodopa for instance will demonstrate lower DAT level using similar SPECT DAT imaging techniques. Early PD patients may have normal DAT SPECT imaging studies despite have clinically convincing PD, suggesting DAT SPECT imaging has limited sensitivity in early PD. This reviewer’s concern is that diseases like DLB and atypical parkinsonian syndromes have a SPECT imaging pattern of generalized reduction of tracer uptake. The sponsor should demonstrate in healthy individuals, patients with ET and Alzheimer’s disease will not be misclassified based on the down regulation caused by levodopa or dopamine agonists.

Review Criteria for Priority Status (MAPP)

Priority (P) review — Preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including *nondrug* products or therapies. Significant improvement is illustrated by the following examples: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation. Although such evidence can come from clinical trials directly comparing a marketed product with the investigational drug, a priority designation can be based on other scientifically valid information.

Conclusion Regarding Priority Review Status

Recommendation

I recommend granting priority review status.

It appears that DaTSCAN is able to image DAT in presynaptic nerve terminals, and indicate presynaptic nerve terminal loss above some undefined threshold. Most patients with Parkinsonian movement disorders will present for medical care after their symptom manifest therefore, specificity is important in this case. Sensitivity and specificity are equally important for patients with clinically uncertain early PD. Preliminary review of the application suggests that DaTSCAN has the potential to enhance the ability to distinguish idiopathic Parkinson’s disease and Essential Tremor. It may also enhance the ability to clinically establish a diagnosis of idiopathic Parkinson’s

disease in its early stages, but the sensitivity is in doubt. In cases where early clinical symptoms of PD are present but DaTSCAN imaging is normal, there is no benefit. DaTSCAN should not be used as the solely method to diagnose a particular neurologic disease. However, the supporting information provided by DAT SPECT imaging may have a significant impact on decision making in specific subsets of patients. The issue of possible effects caused by confounding medications and their potential impact on the results of the individual efficacy trials is a matter for review. Likewise, the acceptability of the sensitivity limits of DaTSCAN to detect the loss of presynaptic DAT in patients with early PD is also a review issue. The initial review of the proposed indication appears too broad compared to the supporting data.

Question 2a

Please address whether, and to what extent clinical diagnosis of Parkinson’s syndrome (PS) and other disorders (Dementia with Lewy Bodies) at the time of imaging or at 18 to 36 months can be used as a “Truth Standard” for striatal dopaminergic deficit (SDD).

The diagnosis of Parkinson’s disease (PD) is determined on clinical grounds. Typically, the diagnosis is established by selective clinical exam criteria. Most often the criteria selected is the UK Parkinson’s Society Brain Bank criteria¹. In patients with early PD, it may be difficult to diagnosis PD with certainty, especially if patients only present with a single cardinal symptom. Because PD is a progressive neurodegenerative disorder patients will develop additional symptoms with the passage of time. Eventually most, but not all patients will meet clinical criteria to establish a diagnosis of PD. Still some diseases may be indistinguishable from PD for sometime after the first symptoms manifest. The UK Parkinson’s Disease Society Criteria that make use of the persistence of PD symptoms over time as a diagnostic feature are “a clinical course of 10 years or more or a “Levodopa response for 5 years or more”, both require a period of observation that is impractical for clinical trial purposes. The National Institute of Neurological Disorders and Stroke (NINDS) put forth another set of clinical diagnostic criteria². The item in the NINDS scale that is dependent on a persistence of PD symptoms, requires the cardinal features of PD persist for at least ≥ 3 years. In fact, the European regulatory authorities have a post-marketing commitment from the sponsor to study DaTSCAN in patients in a clinical trial requiring 3 years of clinical follow up. This study requires the sponsor follow patients using serial DaTSCAN SPECT imaging and clinically exam by a trained movement disorders expert. However, the persistence of symptoms such as tremor alone is insufficient to distinguish essential tremor (ET) for instance from PD. In clinical trials, the accuracy of the clinical diagnosis of PD made by trained movement disorders experts is approximately 89%⁵.

The diagnosis of Dementia with Lewy Bodies (DLB) is difficult to distinguish from other causes of dementia such as Alzheimer’s disease. It is also difficult using clinical criteria to distinguish the motor symptoms associated with DLB from other Parkinsonian syndromes. Even when consensus criteria are applied, the sensitivity of making a diagnosis of DLB using these criteria is low. Autopsy evidence is the only method of

establishing a diagnosis of definite DLB. The symptoms of Parkinsonism and dementia should start within one year of each other in suspected cases of DLB⁶.

Answer To Question 2a

Clinical examination is the method used to establish the diagnosis of PD in patients. It can be difficult to distinguishing early PD from other movement disorders on clinical grounds alone. In clinical practice, performing follow-up exams on patients after a period of time has elapsed is usually how the diagnosis of PD is established,. A diagnosis of PD becomes more certain once other cardinal features of PD emerge with the passage of time. Response to anti-parkinsonian medication is not reliable because the symptoms of other atypical parkinsonian syndromes may also respond to medications used to treat idiopathic PD⁵. The changes in clinical exam over 36 months serving as a “standard of truth (SOT) to determine a final clinical diagnosis of PD, has potential for error but it is a practical standard for this type of clinical trial. Autopsy results would serve as a true SOT, but this is not practical in early PD trials. The availability of 3 year data may improve on the level of diagnostic accuracy but it seems unlikely that this would result in change in diagnosis for a significant number of patients followed for 36 months.

In the case of DLB, elapsed time alone will not definitively establish a diagnosis of DLB disease. The application of consensus clinical criteria and over a 36 month period is also not definitive³. The diagnosis of “Probable DLB” may be confounded by the diagnosis of dementia associated with PD, which appears to be clinically distinct for DLB. Finally, studies using neuropathological criteria for classifying dementia acknowledge there may be overlapping pathology of DLB and Alzheimer’s dementia. In this reviewer’s opinion, clinical means alone should not serve as a gold standard to confirm an imaging diagnosis of DLB.

Question 2b

Please provide a general opinion regarding the strength of the clinical and supportive data in the NDA and as feasible, in the preparation for an advisory committee.

Clinical development Program

GE Healthcare has completed a total of 8 European clinical studies on DaTSCAN: one Phase 1 (CY95.FP.I), two Phase 2 (CY96.FP.II and PDT02005), four Phase 3 (DP008-003, PDT03004 [aka PDT304], PDT301, PDT03007) and one Phase 4 (PDT408). Of these studies, three have been deemed principal to support US registration of DaTSCAN_ for the proposed indication, namely DP008-003, PDT03004 (aka PDT304) and PDT301, with the addition of data to be provided from an investigator-initiated imaging-clinicopathological correlation study [Walker et al. 2007] in patients with along with a literature summary. Collectively, 942 subjects were dosed with DaTSCAN in the clinical

development program. There is also an ongoing Phase 4 trial (PDT408), which has enrolled 174 of 250 planned subjects as of 26 September 2008.

Tabular Listing of Supporting Clinical Trials

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Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT02005 (continued)		profile in subjects, following a single intravenous (i.v) injection of DaTSCAN™.						
Efficacy and Safety	DP008-003 US	[5.3.5.1]	Revised for US: Primary: Sensitivity and specificity for detecting or excluding a SDD. Secondary: Inter-reader agreement	Phase 3. Multicenter. Comparator-group. Open-label. Non-controlled. Non-randomized. No control.	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	224	Healthy subjects (35) Parkinsonian syndrome patients (160) Essential tremor patients (29)	1 dose	Complete; full
Efficacy and Safety	DP008-003 EU	[5.3.5.1]	Primary: To determine the sensitivity and specificity of striatal uptake of [¹²³ I]FP-CIT (DaTSCAN™) in patients with a clinical diagnosis of PD, MSA and PSP compared with ET. Secondary: To assess safety parameters (hematology, biochemistry and urinalysis, vital signs and ECG), and the adverse event profile in patients/volunteers following a single intravenous injection of [¹²³ I]FP-CIT (DaTSCAN™). To assess the striatal uptake of [¹²³ I]FP-CIT (DaTSCAN™) in healthy volunteers as a means to facilitate the calibration of imaging equipment at each study site.	Phase 3. Multicenter. Comparator-group. Open-label. Non-controlled. Non-randomized. No control.	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	224	Healthy subjects (35) Parkinsonian syndrome patients (160) Essential tremor patients (29)	1 dose	Complete; full
Efficacy and Safety	PDT03004 US (aka PDT304)	[5.3.5.1]	Revised for US: Primary: Sensitivity and specificity for detecting or excluding a SDD. Secondary: Inter-reader agreement	Phase 3. Multicenter. Open-label. Non-comparative. Non-randomized. Repeat administration. No control.	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	179	Parkinson's disease patients (71) Non-Parkinson's disease patients (31) Patients with no diagnosis (77)	3 single doses, 18 months apart	Complete; full
Efficacy and Safety	PDT03004 EU (aka PDT304)	[5.3.5.1]	Primary: To determine the predictive value of DaTSCAN™ SPECT to differentiate between subjects with early features of Parkinsonism, other causes of tremor (mainly ET), and healthy volunteers.	Phase 3. Multicenter. Open-label. Non-comparative. Non-randomized. Repeat	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	179	Parkinson's disease patients (71) Non-Parkinson's disease patients (31) Patients with no diagnosis (77)	3 single doses, 18 months apart	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT03004 EU (aka PDT304) (continued)		Secondary: To determine if changes in DaTSCAN™ SPECT are representative of the progression in clinical symptomatology over 36 months. To assess safety parameters and the adverse event profile in subjects following a single intravenous injection of DaTSCAN™.	administration: No control.					
Efficacy and Safety	PDT03007	[5.3.5.1]	Primary: To investigate the change in the uptake of DaTSCAN™ after two years, in healthy volunteers and subjects with Parkinsonian Syndrome and essential tremor, by SPECT imaging. Secondary: To assess the safety parameters (haematology, biochemistry and urinalysis, vital signs and ECG), and the adverse event profile in subjects following a single intravenous (i.v) injection of DaTSCAN™.	Phase 3. Multi-center. Open-label. Non-randomized. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	31	Healthy subjects (8) Parkinsonian syndrome patients (20) Essential tremor patients (3)		Complete, full
Efficacy and Safety	PDT301 US	[5.3.5.1]	Revised for US: Primary: Sensitivity and specificity for detecting or excluding a SDD. Secondary: Inter-reader agreement	Phase 3. Multi-center. Open-label. Non-randomized. Single-dose. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	326	Dementia patients (326)	1 dose	Complete, full
Efficacy and Safety	PDT301 EU	[5.3.5.1]	Primary: 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 of an independent CP used as the standard of truth. Secondary: To determine the accuracy, positive predictive value, and negative predictive value of DaTSCAN™ SPECT visual assessment findings when compared to the clinical diagnosis (i.e., probable DLB/ non-DLB) of the CP as the SOT. To compare the results of semi-	Phase 3. Multi-center. Open-label. Non-randomized. Single-dose. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	326	Dementia patients (326)	1 dose	Complete, full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT301 EU (continued)		quantitative analysis of the striatal uptake ratios of DaTSCAN™ SPECT images between probable, possible, and non-DLB in specific regions of interest (i.e., striatum, caudate, and putamen in both hemispheres). To assess the impact of DaTSCAN™ SPECT visual assessment findings on the on-site investigator's ability and level of confidence to establish a diagnosis and to make a management decision. To assess the proportions of abnormal DaTSCAN™ SPECT visual assessment findings in relation to the groups of 'probable DLB', 'possible DLB', and 'non-DLB'. To review the efficacy analysis via the re-assessment of the clinical diagnosis established by the CP after a 12-month follow-up period. To confirm the safety profile of a single i.v. injection of DaTSCAN™ in the subject population.						
Efficacy and Safety	PDT408 US	[5.3.5.1]	Revised for US: Primary: Impact of DaTSCAN™ image assessments on patient diagnoses, confidence that patient had PS, and planned management.	Phase 3b/4. Multi-center. Open-label. Non-comparative. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	120	Parkinsonian syndrome patients (120)	1 dose or, 2 doses, 24 months apart	Complete, full
Efficacy and Safety	PDT408 EU	[5.3.5.1]	Primary: To assess the striatal uptake of DaTSCAN™ SPECT in subjects with clinically uncertain PS to help in the differentiation between 'PS' (i.e. associated with dopaminergic deficit, including idiopathic PS, MSA, PSP or other true Parkinsonian disorders) and 'non-PS' (i.e. other movement disorders). Secondary: To assess the ability of DaTSCAN™ SPECT imaging to increase diagnostic confidence in PS.	Phase 3b/4. Multi-center. Open-label. Non-comparative. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	120	Parkinsonian syndrome patients (120)	1 dose or, 2 doses, 24 months apart	Complete, full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	GE-001-Walker EU	[5.3.5.1]	<p>Objectives of the first, cross-sectional stage of the study: To compare DaTSCAN™ radio-uptake ratios in the caudate nucleus, anterior and posterior putamen as determined by semi-quantitative, ROI based image assessment in patients with the clinical diagnoses of DLB, PD and AD and in controls. The baseline clinical diagnosis as established by an old age psychiatrist following a comprehensive clinical, neurological and neuropsychiatric examination and based on internationally accepted diagnostic criteria served as a reference standard for the cross-sectional study phase.</p> <p>Objectives of the second, longitudinal stage of the study: To determine the sensitivity and specificity of the ROI-based semi-quantitative analysis of DaTSCAN™ radio-uptake ratios in the caudate nucleus, anterior and posterior putamen when compared to the neuropathological diagnosis at autopsy as the SOT. To determine the sensitivity and specificity of the visual assessment of the DaTSCAN™ images analyzed by 3 readers (in consensus who were blinded to all clinical information) when compared to the neuropathological diagnosis at autopsy as the SOT. To determine the sensitivity and specificity of the clinical diagnosis (reference standard of the cross-sectional study phase) when compared to the neuropathological diagnosis at autopsy as the SOT.</p>	Investigator-initiated. Proof-of-concept. Open-label. Cross-sectional. Longitudinal.	DaTSCAN™, single injection containing approximately 150-185 MBq (4-5 mCi); intravenous injection	80	Alzheimer's disease patients (17) Parkinson's disease patients (19) Dementia with Lewy bodies patients (27) Cortico-basal degeneration patients (1) Healthy subjects (16)	1 dose	Ongoing; interim

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT408 EU (continued)		<p>To identify possible cases where DaTSCAN™ SPECT imaging had impact on patient management. To assess the adverse event profile in subjects following a single intravenous injection of DaTSCAN™.</p>						
Efficacy	PDT409		<p>Primary: To assess the influence of DaTSCAN™ imaging on the clinical management of subjects with clinically uncertain parkinsonism. Secondary: To assess the influence of DaTSCAN™ imaging on the diagnosis of subjects with clinically uncertain parkinsonism. To assess changes in diagnostic confidence after DaTSCAN™ imaging. To describe healthcare resource use (HRU) from baseline to follow up. To explore the influence of DaTSCAN™ imaging on the Quality of Life (QoL) from baseline to follow up.</p>	Phase 4. Multi-center. Open-label. Randomized. Comparative. Non-dosed control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	250 (planned)	Clinically uncertain Parkinsonism patients.	1 dose	Ongoing; none
Efficacy	GE-001-Walker US	[5.3.5.1]	<p>Revised for US: To determine the sensitivity and specificity of: The visual assessment of DaTSCAN™ images based on the consensus of three readers who were blinded to all clinical information compared to the neuropathological diagnosis at autopsy (standard of truth in the longitudinal phase) The baseline clinical diagnosis (the SOT of the cross-sectional phase of the study) compared to the neuropathological diagnosis at autopsy (the SOT in the longitudinal phase) ROI-based semi-quantitative analysis of DaTSCAN™ radioactivity uptake ratios in each striatum (specifically, the caudate nucleus and the anterior and posterior putamen) compared to the neuropathological diagnosis at autopsy (the SOT in the longitudinal phase)</p>	Investigator-initiated. Proof-of-concept. Open-label. Cross-sectional. Longitudinal.	DaTSCAN™, single injection containing approximately 150-185 MBq (4-5 mCi); intravenous injection	80	Alzheimer's disease patients (17) Parkinson's disease patients (19) Dementia with Lewy bodies patients (27) Cortico-basal degeneration patients (1) Healthy subjects (16)	1 dose	Ongoing; interim

PD Versus Non-PD Diagnosis (Reviewer Comment)

The clinical trials have a primary endpoint of sensitivity and specificity. The design is open label, using blinded raters, on site and blinded central readers for the SPECT images. Clinical rating was conducted by blinded movement disorders experts viewing videotaped exams supplemented with some clinical data.

Summary of results of the primary endpoint of pivotal studies in patients with early PD versus non-PD indicate a low sensitivity. This is due to patients with normal SPECT Scans in patients who have early PD based on SOT clinical exam. The specificity of detecting SDD has a median value of 97% at baseline and at 36 months. At baseline when most patients would present for diagnosis the specificity would aid in distinguishing PD from other non-PD disorders.

Summary of Sensitivity and Specificity by Clinical Diagnosis—Blind Image Reads (Sponsor’s text) Pooled Analysis

Sensitivity and specificity were summarized from for all 4 principal studies. Because no blinded read was conducted in study PDT408, the data from that study are not included in pooled analyses of blinded read data. For detecting a symptomatic dopaminergic deficit in the pooled ITD population for subjects with symptoms of a *movement disorder* (where the clinical context would allow differentiation between SDD-related conditions such as PS/PD and non-SDD related conditions such as ET), the sensitivity of individual blind readers at baseline ranged from a low of 75.0% to a high of 96.8%, and the specificity ranged from 80.6% to 96.8%. Results were comparable at 12, 18, and 36 months for those studies that included these time points. The mean results for sensitivity across all readers were 91.1% (95% CI = 89.2, 92.8) at baseline, 78.9% (72.8, 84.2) at month 18, and 76.6% (70.1, 82.3) at month 36. For specificity, the mean results for all readers were 92.3% (89.3, 94.7) at baseline, 95.7% (89.2, 98.8) at month 18, and 96.7% (90.6, 99.3) at month 36.

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Table 13 Summary of Sensitivity and Specificity by Expert Clinical Diagnosis—Individual Blind Reads—ITD Population All Subjects (N = 726)

Response	Expert Clinical Diagnosis (SOT)					
	Parkinsonian Syndrome (PS; SDD)		Dementia with Lewy Bodies (DLB; SDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Study DP008-003						
Reader A	93.0% (87.9, 96.5)	93.5% (84.3, 98.2)				
Reader B	96.8% (92.8, 99.0)	80.6% (68.6, 89.6)				
Reader C	96.2% (91.9, 98.6)	91.9% (82.2, 97.3)				
Reader D	92.4% (87.1, 96.0)	96.8% (88.8, 99.6)				
Reader E	94.3% (89.5, 97.4)	91.9% (82.2, 97.3)				
Study PDT03004 (aka PDT304) - Baseline						
Reader A	77.5% (66.0, 86.5)	96.8% (83.3, 99.9)				
Reader B	77.9% (66.2, 87.1)	96.8% (83.3, 99.9)				
Reader C	78.6% (67.1, 87.5)	96.8% (83.3, 99.9)				
Study PDT03004 (aka PDT304) - Month 18						
Reader A	77.5% (66.0, 86.5)	96.7% (82.8, 99.9)				
Reader B	77.5% (66.0, 86.5)	93.5% (78.6, 99.2)				
Reader C	81.7% (70.7, 89.9)	96.8% (83.3, 99.9)				
Study PDT03004 (aka PDT304) - Month 36						
Reader A	75.0% (63.0, 84.7)	96.7% (82.8, 99.9)				
Reader B	76.9% (64.8, 86.5)	96.7% (82.8, 99.9)				
Reader C	77.9% (66.2, 87.1)	96.7% (82.8, 99.9)				
Study PDT301 - Baseline						
Reader A			79.7% (69.2, 88.0)	91.2% (85.2, 95.4)		
Reader B			75.3% (64.2, 84.4)	88.5% (82.0, 93.3)		
Reader C			80.2% (69.9, 88.3)	90.5% (84.3, 94.9)		

Reviewer Comment

The sensitivity of DaTSCAN appears to offer little or no advantage over clinical diagnosis. The lower bounds of the C.I. for specificity appear to be the same as the estimate of 89% of diagnostic accuracy using clinical criteria alone.

DLB Versus Non-DLB Dementia (Reviewer Comment)

The benefit of DaTSCAN imaging in distinguishing DLB and Alzheimer's dementia appears to be more limited. Both sensitivity and specificity appear to offer little advantage over clinical diagnosis. The Walker study is an investigated initiated supporting study that incorporated autopsy results as the final truth standard in making the diagnosis of DLB versus non-DLB (Alzheimer's dementia). I strongly urge the review team to read the entire published journal article reporting the results of the "Walker" Study. The information regarding classification of SPECT and clinical diagnosis are reported in much more detail in the journal publication compared to the sponsor's study report. There were 22 cases with autopsy results reported along with the DaTSCAN results. In 11 cases (see the table below), the clinical and DaTSCAN diagnosis disagreed. In 4 of the cases (highlighted in yellow), the post-mortem findings proved the DaTSCAN diagnosis were wrong. In another 9 cases, the DaTSCAN and postmortem diagnosis proved the clinical diagnosis was incorrect (red boxed). In 2 of the 9 cases the diagnosis of DLB is questionable (patients #1 and #5) because pathology results indicated mixed AD and DLB pathology. The net result indicates DaTSCAN imaging was not significantly superior in making the correct diagnosis on DLB or non-DLB when compared to the autopsy evidence in cases where the clinical diagnosis may be uncertain. The number of patients in the autopsy series are small with a misleading DaTSCAN imaging results in 18% (n=4) of the cases. In the discussion portion of the paper, the author acknowledges that the clinical diagnosis used for comparison was made by a single examiner at baseline only. Repeat exams suggested the clinical diagnosis should be changed in some cases but only the Baseline diagnosis was included in the comparison. Possibly making the number of errors for DaTSCAN 6 and the number of clinical errors 7. In 2 cases the clinical and DaTSCAN diagnosis were both wrong patients #11 and #17 and they were counter as errors for both the clinical and DaTSCAN diagnosis.

Table 5 Diagnostic Results by Subject

Case No	Gender	Age at DaTSCAN™ Imaging	Post-Mortem Diagnosis	Baseline Clinical Diagnosis	Baseline Clinical Diagnosis Classification	Visual DaTSCAN™ Image Assessment	Visual DaTSCAN™ Image Classification
1	Male	78	DLB	AD	Non-DLB	Abnormal	DLB
2	Male	82	DLB	DLB	DLB	Abnormal	DLB
3	Male	77	DLB	DLB	DLB	Normal	Non-DLB
4	Female	82	DLB	DLB	DLB	Abnormal	DLB
5	Female	58	DLB	CBD	Non-DLB	Abnormal	DLB
6	Female	84	DLB	DLB	DLB	Abnormal	DLB
7	Female	82	DLB	DLB	DLB	Abnormal	DLB
8	Female	69	DLB	DLB	DLB	Abnormal	DLB
9	Female	77	Non-DLB	AD	Non-DLB	Normal	Non-DLB
10	Male	77	Non-DLB	AD	Non-DLB	Normal	Non-DLB
11	Female	76	Non-DLB	DLB	DLB	Abnormal	DLB
12	Male	76	Non-DLB	DLB	DLB	Normal	Non-DLB
13	Male	85	Non-DLB	DLB	DLB	Normal	Non-DLB
14	Male	67	Non-DLB	DLB	DLB	Normal	Non-DLB
15	Male	95	Non-DLB	AD	Non-DLB	Normal	Non-DLB
16	Male	84	Non-DLB	AD	Non-DLB	Normal	Non-DLB
17	Male	68	Non-DLB	DLB	DLB	Abnormal	DLB
18	Male	63	Non-DLB	DLB	DLB	Normal	Non-DLB
19	Male	81	Non-DLB	DLB	DLB	Normal	Non-DLB
20	Female	85	Non-DLB	AD	Non-DLB	Normal	Non-DLB
21	Female	74	Non-DLB	AD	Non-DLB	Normal	Non-DLB
22	Male	86	DLB	DLB	DLB	Normal	Non-DLB

AD = Alzheimer’s disease; CBD =cortico-basal degeneration; DLB = dementia with Lewy bodies.

REF: Section 14.2, Table [4]

Analysis of Pooled Data (Sponsor’s text)

For detecting a SDD in the pooled intention to diagnose (ITD) population for subjects with symptoms of *dementia* (where the clinical context would allow differentiation between SDD-related conditions such as DLB and Parkinson’s disease with dementia [PDD] and non-SDD related conditions such as AD and Vascular dementia (VaD), the sensitivity of individual blind readers at baseline ranged from a low of 75.3% to a high of 82.3%, and the specificity ranged from 88.5% to 91.2%. The results at month 12 were comparable. The mean results across all readers for diagnosis of DLB were, at baseline, 78.5% (72.7, 83.5) for sensitivity and 90.1% (86.8, 92.8) for specificity. At month 12, the mean results for all readers were 78.5% (72.7, 83.5) for sensitivity and 92.8% (89.6, 95.2) for specificity. The submission did not appear to contain data suggesting DaTSCAN could distinguish dementia associated with PD from other causes for dementia.

Reviewer’s Comment

The progressive asymmetric loss of pigmented neurons containing DAT in the striatum is a key pathological feature of Idiopathic Parkinson’s disease. In Atypical Parkinsonian Syndromes (PS), dementia with Lewy bodies (DLB), and other related diseases, dopamine loss in the striatum may not be as prominent and more evenly distributed, making it more difficult to distinguish between these disorders using DAT imaging. DaTSCAN images the Dopamine Transporter (DAT) molecule in pre-synaptic dopaminergic nerve terminals. A similar DAT SPECT imaging agent was incorporated into U.S. Parkinson’s disease clinical drug trials to explore their potential for detecting early PD and their potential to act as a marker for disease progression. The most often

studied DAT SPECT agent studies in U.S. PD trials is 2 beta-carboxymethoxy-3 beta(4-iodophenyl) tropane (beta-CIT). One recognized flaw associated with DAT SPECT (beta-CIT) imaging is a potential confounding effect caused by co-administration of dopaminergic drugs given to treat the symptoms of Parkinson's disease. A frequently cited example of this flaw associated with beta-CIT SPECT is discussed in the results of The ELLDOPA Study (Fahn et al. NEJM 351:249, 2004; PMID: 15590952)⁵. Patients in the ELLDOPA trial treated with carbidopa/levodopa (CD/LD) appeared to have undergone significant dopaminergic neuronal loss observed on beta-CIT SPECT scanning compared to the placebo treated group. However, clinically these patients performed better than placebo treated patients. In addition, some early PD patients had normal beta-CIT SPECT scans initially but were later determined to have PD by clinical observation over time (the sponsor's diagnostic gold standard used in DaTSCAN trials). Once patients in the ELLDOPA trial were washed out from treatment with CD/LD (off levodopa for 2 weeks), they appeared to maintain a symptomatic benefit over the placebo treated group. The clinical observations suggested that levodopa may have a disease modifying benefit contrary to the results of beta-CIT scans suggesting their striatal neuronal loss had progressed. One of the possible explanations is that treatment with levodopa may cause down-regulation of DAT⁴. The finding casts doubt on the notion that DAT imaging is reliable in patients treated with levodopa and potentially other dopaminergic medications. The sponsor counters this argument by stating that drugs affecting the dopamine transporter would be evenly distributed and the effect would not impact the DaTSCAN interpretation. Although, this may be true, it could potentially be a problem in patients who might receive DaTSCAN to evaluate possible ET, Alzheimer's disease and DLB, where a diffuse reduction in DAT imaging may be the typical pattern of abnormality.

The data presented by the sponsor and by Walker seems to assume that animal data and data from non-demented, patients with normal striatum is adequate to assume dopaminergic medications do not affect DaTSCAN results. Given the considerable human experience using Beta CIT SPECT DAT imaging this assumption may not be valid and the sponsor should provide patient data to establish the DaTSCAN is not affected by dopaminergic medications.

Methods Sections of The Walker Publication.

“Two patients were taking levodopa medication and three patients were taking neuroleptic medication at the time of scanning. One patient took sulpiride 200 mg at night and two patients took olanzapine 5 mg/day. These medications were not discontinued because they do not interfere with dopamine transporter imaging¹³⁻¹⁶”

Classification of Clinical, Imaging and Neuropathology Findings

In the methods section of the Walker publication, the authors state “subjects were recruited into the study from 1996 to 1999”. Consensus criteria to make a DLB diagnosis were versions that were available at the time subjects were recruited into the trial. The consensus criteria for clinical diagnosis of DLB have undergone substantial revision since the mid-1990's which may not reflect the current sensitivity and specificity estimates for making a correct clinical diagnosis of DLB.

The authors also describes the clinical classification of patients with DLB used for their study purposes :

“At that time, autopsy results were available for 10 of the cases and were reported briefly. In the original cohort, patients with dementia were ascribed to either the DLB or AD group on the basis of fulfilling the Consensus DLB criteria¹² or NINCDS-ADRDA

criteria.11 Many of the patients with DLB fulfilled both sets of criteria, and these patients were classified as having DLB”.

By “fulfilling both sets of criteria”, I assume the authors mean fulfilling for both DLB and AD.

Reviewer Comment

Clinically, subjects who met criteria for both AD and DLB were classified as DLB however it is not clear how this decision was made. A patients with 1 core feature of DLB was clinically classified as DLB (patient #17) and patients #5 and #15 also had 1 core feature of DLB but were not clinically classified as having DLB.

Table 3 Initial clinical, imaging and autopsy diagnosis
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Case #1 the clinical diagnosis was reported as AD but the neuropathological diagnosis was reported as mixed AD + DLB but under the authors classification scheme this patient was reported as a case of DLB. The CERAD and Braak staging (score 5/6 is considered severe) indicated the presence of significant AD pathology mixed with (intermediate pathologic criteria for) DBL. All other cases with Braak stage 5-6 neuropathology were classified as having AD. In case 1 there was also disagreement among the scan raters regarding the assignment of the scan as normal or abnormal. The authors describe this patient as not having any of the clinical core features of DLB at baseline. This case illustrates the difficulty caused by patients who may have mixed pathology, AD, DBL and vascular dementia. The majority of patients in the study who came to autopsy had mixed pathology results.

Case#5 The clinical diagnosis was cortico-basal degeneration (CBD) with a neuropathological diagnosis of mixed pathology DBL + AD. This patient was also given a final diagnosis was DBL. This case also reported conflicting DaTSCAN results, which were reported as abnormal on visual scan but normal on semiquantitative DaTSCAN. The author reports the semiquantitative scan result as being more accurate (specific). In this case the semi-quantitative scan would indicate a non-DLB diagnosis. The CERAD classification for the neuropathology findings were listed as “definite AD” with a high Braak classification score for AD pathology.

Table 4 Neuropathological diagnosis and diagnostic criteria
Copyright Material

The full journal publication of the Walker study (see reference below) included the complete discussion section, which is not included in the references provided by the sponsor.

Walker Z, Jaros E, Rodney, Walker WH, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy J Neurol Neurosurg Psychiatry 2007;78:1176–1181.

Authors Conclusions Excerpt From The Discussion Section

“An abnormal FP-CIT SPECT scan, as defined in this study, equates to a bilateral lesion of the dopaminergic neurons projecting from the substantia nigra to the

striatum, specifically to the putamen. Clearly, the commonest cause of this is idiopathic PD. The same abnormality is to be expected, and is indeed found, in PD with dementia.⁶ An abnormal scan is not specific for LB pathology. How reliably it identifies patients with DLB will depend on the population of patients tested. For instance, PD and multiple systems atrophy cannot be distinguished by FP-CIT SPECT. Ordinarily, multiple systems atrophy is not characterised by dementia and so will not be a source of false positives. There are however some (mainly rare) neurological disorders which might be expected to give “false positive” results, reducing the specificity of the test. These might include vascular parkinsonism with dementia, and other forms of parkinsonism with dementia such as CBD, progressive supranuclear palsy, frontotemporal dementia with parkinsonism linked to chromosome 17 and Creutzfeldt–Jakob disease. In some of these conditions the main striatal dopaminergic lesion is however postsynaptic rather than presynaptic. Multiple pathologies represent another important possible cause of false positive scan results. PD is common. Incidental or presymptomatic nigral LB disease at autopsy is also not uncommon. It must be possible for patients to have, for instance, AD and also have PD or incidental nigral LB disease without having diffuse LB disease. Autopsies of such cases have been reported.²⁵ In such cases, FP-CIT binding in the caudate would be expected to be relatively preserved²³ but both visual and semiquantitative rating of putaminal binding would give an abnormal scan result. Widespread use of FP-CIT scans in very large numbers of patients with unselected dementia would be expected to generate a number of false positive results. It goes without saying that scanning is no substitute for careful clinical assessment of patients”.

Reviewer Comment

Recent reports estimate the prevalence of PD associated dementia at approximately 52%⁷. The clinical entities described by the author may be uncommon in the general population but in a selected patient population presenting with dementia and Parkinsonian symptoms the likelihood of encountering patients with vascular Parkinsonism, multisystem atrophy, Progressive Supranuclear Palsy or PD related dementia is likely. By the author’s own admission DaTSCAN can not reliably differentiate these disorders from DLB.

“FP-CIT SPECT scanning performed considerably better than clinical criteria as a means of supporting the diagnosis of DLB in patients with dementia. It correlated very well with the presence of LB pathology at autopsy, even with a gap of nearly 3 years, on average, between scan and autopsy (see table 2). It clearly supports the recent change made in the Revised clinical criteria for the diagnosis of DLB²¹ which now includes “low dopamine transporter uptake in the basal ganglia demonstrated by SPECT imaging” as a “suggestive feature” for DLB ‘.

However the authors admit that that they do not compare the clinical diagnosis followed over time to the DaTSCAN imaging results. The clinical diagnostic impression over a 36 month period was the SOT for establishing a diagnosis of PD. It seems strange that the authors would not compare the DaTSCAN results to the clinical established over a period of time rather than using only the baseline clinical diagnosis. This approach seems to bias against making an

accurate clinical diagnosis, since by definition the clinical criteria used to diagnosis DLB requires symptoms dementia and PD or autonomic failure to begin with in one year of each other. The symptoms must fluctuate over time, the clinical features are expected to change with time change.

Walker Journal Article Comments By The Authors.

“At follow-up, the clinical diagnosis sometimes changed, but for the purpose of this study we used only the baseline diagnosis for analysis of results”.

Answer To Question 2b

The sensitivity of DaTSCAN in some early PD patients of DaTSCAN is limited. The specificity in a select group of patients, who are examined carefully and the differential diagnosis is limited to PD versus ET. DaTSCAN appears to be acceptable for providing additional information to distinguish some patients with early PD. The sponsor’s experience in differentiating idiopathic Parkinson’s disease from multiple system atrophy (MSA) progressive supranuclear palsy (PSP) and psychogenic parkinsonism is too limited clearly determine that DaTSCAN can distinguish between these disorders and PD in their early stages. DaTSCAN imaging becomes unnecessary, once the symptoms of these atypical parkinsonian syndromes declare themselves clinically. When autopsy data is used as the gold standard of evidence, the data does not support the notion that DaTSCAN imaging is superior to clinical diagnosis, for distinguishing DLB from non-DLB.

The sponsor should also supply evidence that anti-parkinsonian drugs (at least levodopa and dopamine agonists) do not affect DaTSCAN imaging or that adjustments can compensate for these changes.

References

1. Hughes AJ, Daniel SE, Kilford L, et al. Accuracy of clinical diagnosis of idiopathic Parkinson’s disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psych.* 1992;55:181-184.
2. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson disease. *Arch Neurol* 1999;56:33–9.
3. Guttman M, Stewart D, Hussey D, Wilson A, Houle S, Kish S. Influence of L-dopa and pramipexole on striatal dopamine transporter in early PD. *Neurology* 2001;56:1559- 64.
4. The Parkinson Study Group Levodopa and the Progression of Parkinson’s Disease. *N Engl J Med* 2004;351:2498-508.
5. The diagnosis of Parkinson’s disease. Eduardo Tolosa, Gregor Wenning, Werner Poewe *Lancet Neurol* 2006; 5: 75–86.

6. McKeith, IG, Dickson, DW, Lowe J. Diagnosis and management of dementia with Lewy bodies Third report of the DLB consortium Neurology 2005;65:1863–1872.
7. Riedel O, Klotsche j, Spottke a, ET AL. Cognitive impairment in 873 patients with idiopathic Parkinson’s disease Results from the German Study on Epidemiology of Parkinson’s Disease with Dementia (GEPAD)J Neurol (2008) 255:255–264

Gerald D. Podskalny, D.O.
Medical Reviewer – DNDP ODE I

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Gerald D Podskalny

6/8/2009 09:56:18 AM

MEDICAL OFFICER

Revised DNP consult with additional information

DSI CONSULT: Request for Clinical Inspections

Date:

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1, HFD-46
Joe Salewski., Branch Chief (Acting), GCP2, HFD-47
Name of DSI Primary Reviewer (if known)

Through: Phillip Davis, Clinical Reviewer, Division of Medical Imaging and Hematology, HFD-160
Liberio Marzella, Clinical Team Leader, Division of Medical Imaging and Hematology, HFD-160

From: James Moore, Regulatory Health Project Manager/Division of Medical Imaging and Hematology Products/HFD-160

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-454

Sponsor contact information: GE Healthcare - Allison Mueller (609-514-6843)

Drug: DaTSCAN® (I¹²³) Ioflupane

NME: Yes

Priority Yes

Study Population: Patients with signs & symptoms of movement disorders, dementia & healthy controls.

Pediatric exclusivity: No

PDUFA: September 9, 2009

Action Goal Date: September 8, 2009

Inspection Summary Goal Date: August 12, 2009

II. Background Information

Include a brief introduction about the application and include the following:

- New application NDA 22-454 (new molecular entity)
- Proposed indication: 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.

- DaTSCAN is a ¹²³I labeled cocaine analog which binds to the dopamine transporter protein (DaT) found in the axon terminals (located in striatum) of pre-synaptic nigrostriatal neurons in the brain. Imaging DaTSCAN binding to DaT proteins in the brain by SPECT is 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 age-related loss of nigrostriatal neurons. DaTSCAN is administered by intravenous injection with a proposed dose of 5 millicuries, which contains approximately 0.3 micrograms of ioflupane.
- If approved, DaTSCAN would be the first product available for the diagnosis of loss of functional dopaminergic neurons in the brain. DaTSCAN would be used in patients with signs and symptoms of movement disorders and dementia in order to detect or exclude the loss of functional dopaminergic neurons in the brain. This would assist clinicians in diagnosing or excluding Parkinson’s disease and Parkinsonian Syndromes, as well as Dementia with lewy bodies in patients presenting with signs & symptoms of movement disorders or dementia.
- The below table provides the pivotal studies submitted for DaTSCAN safety and efficacy.

Study Number, Number of study centers Location(s)	Study period, No. of subjects planned/enrolled, Dosing	Design, Standard of truth (SOT), Image analysis method (IAM)	Primary endpoint
Phase III trials			
DP008-003 6 centers in Europe	8/25/1997 to 2/24/1998 186 subjects planned (146 patients & 36 healthy volunteers), Single dose 3 – 5 mCi	Multi-center, open-label, non-randomized, SOT = expert clinical diagnosis at baseline by consensus criteria IAM = On site blinded image evaluation (BIE) by 5 of the study investigators	Sensitivity and specificity in patients diagnosed with PS involving SDD (PD, MSA, PSP) compared with patients with ET (no SDD present)
PDT304 10 centers in Europe participated.	1/18/1999 to 6/28/2005 180 subjects planned, 202 enrolled, 179 received study drug, 179 evaluable for safety evaluation (after 1 st dosing), 102 evaluable for efficacy (PP) at T= 36 months 3 totals doses: DaTSCAN 3-5 mCi at 3 separate time points (T=0, T=18 & T=36 months).	Multi-center, open- label, non-randomized, single dose clinical trial SOT = consensus diagnosis established by 2 independent movement disorder specialists (MDS) by taped video assessment (T= 36 months), IAM = BIE by 3 independent readers a ^{(b) (4)}	To determine the predictive value of DaTSCAN SPECT images in differentiating between subjects with early features of PS, other causes of tremor (ET) and healthy volunteers.

<p>PDT408 15 centers in Europe participated.</p>	<p>11/21/2000 to 11/14/2003, 125 enrolled, 120 evaluable for safety, 118 evaluable for efficacy Follow-up assessment: 118 eligible, 33 excluded (7 died, 26 lost to f/u), 85 evaluable, 78 received diagnosis at 24 months, 14 re-imaged with DaTSCAN 3-5 mCi DaTSCAN @ baseline, with some repeated dosing @ 24 months</p>	<p>Multi-center, phase 3b/4, open-label, non-randomized, clinical trial SOT = investigator's clinical diagnosis at 24 months IAM = Image analysis by on-site nuclear medicine physician</p>	<p>To assess the striatal uptake of DaTSCAN in subjects with clinically uncertain Parkinsonian symptoms to help in the differentiation between Parkinsonian syndromes (PS) (SDD present) and non-PS (no SDD present).</p>
<p>PDT301 40 centers in Europe participated</p>	<p>12/21/2003 to 6/28/2006 320 subjects planned, 351 enrolled, 327 received study drug, 326 evaluable for safety (ITD), 288 evaluable for efficacy (PP) Single dose DaTSCAN 3-5 mCi</p>	<p>Multi-center, open-label, non-randomized, single dose clinical trial SOT = expert clinical diagnosis as established by consensus panel at 12 month follow-up. IAM = BIE at image review center [REDACTED] (b) (4)</p>	<p>To determine the sensitivity and specificity of the visual assessment of DaTSCAN images in differentiating between patients with DLB and patients with non-Lewy body dementia.</p>
<p>Walker Study 12 investigators at one study site in the UK participated. (all image interpretations performed at Univ. College London Med. School)</p>	<p>6/1996 to 12/1999, autopsy phase ongoing 22 subjects in AD, PD, & controls group planned, 40 planned in DLB group, 80 subjects enrolled: 17 AD, 19 PD, 27 DLB, 1 diagnosed with "other", 16 controls Single dose DaTSCAN 3-5 mCi</p>	<p>Investigator-initiated, single-center, open-label, non-randomized, clinical trial 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.</p>	<p>To determine the sensitivity and specificity of: 1. Visual, assessment of DaTSCAN images compared to neuropathological diagnosis (SOT) at autopsy in patients with diagnosis of PD, DLB, AD & in controls.</p>

III. Protocol/Site Identification

Include the Protocol Title/# for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
<p>Site # 23</p> <p>Southampton Memory Assessment & Research Center, Moorgreen Hospital, Botley West End, Southampton, Hampshire, S030 3JB, UK EMAIL: c.holmes@soton.ac.uk Principal Investigator: Dr. Clive Holmes Fax 44 2380 796927 Sub Investigator: (b) (4)</p>	<p>PDT301 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.</p>	<p>18 enrolled/ 17 received study drug</p>	<p>(b) (4)</p>
<p>Site # 26</p> <p>Neurologia 2, Spedali Civili di Brescia, Piazzale Ospedale, 1 I-25123 Brescia, Italy Phone: ++ 39 030 3995 631 (or 632, 634) EMAIL: padovani@med.unibs.it Fax: ++39 030 3995 027 Principal Investigator: Professor Padovani Sub Investigators: (b) (4)</p>	<p>PDT301 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.</p>	<p>29 enrolled/ 25 given study drug</p>	<p>Site # 26 enrolled more patients than any other center for study PDT301.</p>

Site # (Name,Address, Phone number, email, fax#)	Protocol #	Number of Subjects	Indication
<div style="background-color: #cccccc; width: 100%; height: 100%; display: flex; align-items: center; justify-content: center;"> (b) (4) </div>	PDT301	235 evaluable for efficacy (PP)	Inspect (b) (4) for adherence to blinded image evaluation protocol.
	PDT304	102 evaluable for efficacy (PP)	Inspect (b) (4) for adherence to blinded image evaluation protocol.

IV. Site Selection/Rationale

- Our request for the above DSI inspections is for a new molecular entity application, which relies solely on European data for demonstrating evidence for efficacy and safety claims. The above sites were selected based on these reasons:
 - Studies/sites selected are considered most important in demonstrating efficacy and safety claims.
 - (site #23, study PDT301)).
 - Site selected enrolled more patients than any other sites for the study (site #26, study PDT301).
 - Imaging review centers for studies PDT301 & PDT304 selected to investigate potential protocol violations related to blinded image evaluation protocol.

Domestic Inspections: Appears this way on original

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision making

- ~~_____~~ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ~~_____~~ Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- ~~_____~~ There are insufficient domestic data
- X Only foreign data are submitted to support an application
- ~~_____~~ Domestic and foreign data show conflicting results pertinent to decision-making
- ~~_____~~ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- X Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

V. Tables of Specific Data to be Verified (if applicable)

N/A

Should you require any additional information, please contact James Moore, *RPM* at Ph: 301-796-1986 or Phillip Davis, *Medical Officer* at Ph: 301-796-4252.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer

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/s/

Rafel Rieves

5/28/2009 05:22:46 PM

Consultation Request

IND (Serial Number)	NDA 22-454 (0000)
Sponsor:	GE Healthcare
Drug:	DaTSCAN [Ioflupane 1123 Injection]
Proposed Indication:	Detecting loss of functional dopaminergic neurons
nigrostriatal	
Material Submitted:	Consult received April 28, 2009
Correspondence Date:	April 22, 2009
Date Received / Agency:	April 24, 2009
Date Review Completed	May 19, 2009
Reviewer:	Gerald D. Podskalny, D.O. Medical Reviewer, DNDP, ODE I

1. Introduction

The Division of Medical Imaging and Hematology Products (DMIHP) requested this consult from the Division of Neurology Products (DNP) regarding an investigational imaging product DaTSCAN [^{123}I]ioflupane. The sponsor for this product and NDA application is GE Healthcare. The consult instructions requested DNP to answer 3 specific questions (1, 2a, 2b). A response to question 1 regarding the sponsor's request for priority review status is considered highly time sensitive. The DNP response to the remaining two questions (2a, 2b) regarding the efficacy data, claim, and assistance with assistance with preparing for an advisory committee is needed for a later date, May 14, 2009.

Drug Product

The drug substance in DaTSCAN is [^{123}I]ioflupane. DaTSCAN is an iodine containing diagnostic radiopharmaceutical for intravenous injection. DaTSCAN is a radio-labeled, cyclotron-produced product with a physical half-life of 13.2 hours, which decays to ^{123}Te by electron capture with the emission of gamma radiation (159 keV). The product is supplied in a 10-mL glass vial closed with a rubber stopper and sealed with an aluminum cap. This diagnostic radiopharmaceutical is administered as a single I.V. injection. All of the clinical trial participants were pre-treated with iodine to block uptake by the thyroid.

Mode of Action

The intracellular target for [^{123}I]ioflupane is the dopamine transporter (DAT) protein, which functions to help the neurons terminate neuronal signaling and recycle dopamine. In vivo animal studies demonstrate specific uptake and retention of [^{123}I]ioflupane in normal striatum (mouse, rat, dog, and monkey). In Parkinsonian animal models produced by administration of toxins such as 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) or 6-hydroxydopamine (6-OHDA) [^{123}I]ioflupane uptake was reduced in the striatum in these animals demonstrating loss of functional nigrostriatal dopaminergic neurons. In humans, the pharmacokinetics of [^{123}I]ioflupane leads to the

uptake and selective retention of the iodine-123 radionuclide within dopaminergic nigrostriatal neurons in the brain. Radioactive decay of the iodine-123 to ^{123}Te emitting gamma radiation can be detected externally using gamma (3 headed) detectors, allowing visualization of the striatum through single photon emission computed tomography (SPECT) imaging.

Recommended Dose The recommended dose is 111 to 185 MBq (3 to 5 mCi).

Potential Need for Thyroid Blockade: In the proposed product label the sponsor instructs prescribers of DaTSCAN to consider blocking the patient's thyroid gland with Potassium Iodide Oral Solution (Lugol's Solution) at least 1 hour prior to receiving DaTSCAN. This consideration is emphasized in patients who may live in Iodine poor areas or have certain medical conditions affecting the thyroid.

Regulatory Status

DaTSCAN has been approved in Europe (EMEA) since 2000 however, the approved indication in the EU is much narrower than the indication requested in the U.S. application. The approved indication in Europe is:

"detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain Parkinsonian Syndromes (PS), in order to help differentiate Essential Tremor from PS related to idiopathic Parkinson's disease (PD), multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). DaTSCAN is unable to differentiate between PD, MSA and PSP. DaTSCAN also indicated to help differentiate probable DLB from Alzheimer's disease. DaTSCAN is unable to discriminate between DLB and PD dementia. "

Consult Question 1

The DMIHP requests evaluation of this application to determine whether it should be reviewed as a priority or standard application based on the following indication:

“DaTSCAN is a radiopharmaceutical containing [^{123}I] 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.”

Review of The Sponsor's Rational For Requesting Priority Review Status.

The sponsor states as part of the rational supporting their request for priority review that DaTSCAN's "Characteristic image patterns allow the facile assessment of a patient's nigrostriatal dopaminergic neuronal function as either normal or abnormal, which assists in the diagnostic work-up of patients with movement and cognitive disorders where loss of this function is suggested by clinically observed signs and symptoms".

In the justification for priority review the sponsor states: "Since the treatment approach for dopamine-deficient disorders (primarily dopamine replacement therapy) is inappropriate when there is no dopamine deficiency, and treatment of psychotic symptoms with neuroleptics is contraindicated when there is a dopamine-deficient state, assessment of the dopaminergic system would be expected to aid determination of the correct treatment pathway for the patient". Patients with atypical parkinsonian syndromes such as Multiple System Atrophy, Progressive Supranuclear Palsy and Dementia with Lewy Bodies may benefit symptomatically from treatment with dopaminergic medications. The claim that "treatment with dopamine replacement in patients with no (or lower deficit compared to PD) dopamine deficit is inappropriate", is inaccurate. The sponsor's justification ignores potential limits of this technology that includes problem of potential down regulation of DAT caused medication used to treat the symptoms of PD. Patients exposed to levodopa for instance will demonstrate lower DAT level using similar SPECT DAT imaging techniques. Early PD patients may have normal DAT SPECT imaging studies despite have clinically convincing PD, suggesting DAT SPECT imaging has limited sensitivity in early PD. This reviewer's concern is that diseases like DLB and atypical parkinsonian syndromes have a SPECT imaging pattern of generalized reduction of tracer uptake. The sponsor should demonstrate in healthy individuals, patients with ET and Alzheimer's disease will not be misclassified based on the down regulation caused by levodopa or dopamine agonists.

Review Criteria for Priority Status (MAPP)

Priority (P) review — Preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including *nondrug* products or therapies. Significant improvement is illustrated by the following examples: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness in a new subpopulation. Although such evidence can come from clinical trials directly comparing a marketed product with the investigational drug, a priority designation can be based on other scientifically valid information.

Conclusion Regarding Priority Review Status

Recommendation

I recommend granting priority review status.

It appears that DaTSCAN is able to image DAT in presynaptic nerve terminals, and indicate presynaptic nerve terminal loss above some undefined threshold. Most patients with Parkinsonian movement disorders will present for medical care after their symptom manifest therefore, specificity is important in this case. Sensitivity and specificity are equally important for patients with clinically uncertain early PD. Preliminary review of the application suggests that DaTSCAN has the potential to enhance the ability to distinguish idiopathic Parkinson's disease and Essential Tremor. It may also enhance the ability to clinically establish a diagnosis of idiopathic Parkinson's disease in its early stages, but the sensitivity is in doubt. In cases where early clinical

symptoms of PD are present but DaTSCAN imaging is normal, there is no benefit. DaTSCAN should not be used as the solely method to diagnose a particular neurologic disease. However, the supporting information provided by DAT SPECT imaging may have a significant impact on decision making in specific subsets of patients. The issue of possible effects caused by confounding medications and their potential impact on the results of the individual efficacy trials is a matter for review. Likewise, the acceptability of the sensitivity limits of DaTSCAN to detect the loss of presynaptic DAT in patients with early PD is also a review issue. The initial review of the proposed indication appears too broad compared to the supporting data.

Question 2a

Please address whether, and to what extent clinical diagnosis of Parkinson’s syndrome (PS) and other disorders (Dementia with Lewy Bodies) at the time of imaging or at 18 to 36 months can be used as a “Truth Standard” for striatal dopaminergic deficit (SDD).

The diagnosis of Parkinson’s disease (PD) is determined on clinical grounds. Typically, the diagnosis is established by selective clinical exam criteria. Most often the criteria selected is the UK Parkinson’s Society Brain Bank criteria¹. In patients with early PD, it may be difficult to diagnosis PD with certainty, especially if patients only present with a single cardinal symptom. Because PD is a progressive neurodegenerative disorder patients will develop additional symptoms with the passage of time. Eventually most, but not all patients will meet clinical criteria to establish a diagnosis of PD. Still some diseases may be indistinguishable from PD for sometime after the first symptoms manifest. The UK Parkinson’s Disease Society Criteria that make use of the persistence of PD symptoms over time as a diagnostic feature are “a clinical course of 10 years or more or a “Levodopa response for 5 years or more”, both require a period of observation that is impractical for clinical trial purposes. The National Institute of Neurological Disorders and Stroke (NINDS) put forth another set of clinical diagnostic criteria². The item in the NINDS scale that is dependent on a persistence of PD symptoms, requires the cardinal features of PD persist for at least ≥ 3 years. In fact, the European regulatory authorities have a post-marketing commitment from the sponsor to study DaTSCAN in patients in a clinical trial requiring 3 years of clinical follow up. This study requires the sponsor follow patients using serial DaTSCAN SPECT imaging and clinically exam by a trained movement disorders expert. However, the persistence of symptoms such as tremor alone is insufficient to distinguish essential tremor (ET) for instance from PD. In clinical trials, the accuracy of the clinical diagnosis of PD made by trained movement disorders experts is approximately 89%⁵.

The diagnosis of Dementia with Lewy Bodies (DLB) is difficult to distinguish from other causes of dementia such as Alzheimer’s disease. It is also difficult using clinical criteria to distinguish the motor symptoms associated with DLB from other Parkinsonian syndromes. Even when consensus criteria are applied, the sensitivity of making a diagnosis of DLB using these criteria is low. Autopsy evidence is the only method of

establishing a diagnosis of definite DLB. The symptoms of Parkinsonism and dementia should start within one year of each other in suspected cases of DLB⁶.

Answer To Question 2a

Clinical examination is the method used to establish the diagnosis of PD in patients. It can be difficult to distinguishing early PD from other movement disorders on clinical grounds alone. In clinical practice, performing follow-up exams on patients after a period of time has elapsed is how the diagnosis of PD is established. A diagnosis of PD becomes more certain once other cardinal features of PD emerge with the passage of time. Response to anti-parkinsonian medication is not reliable because the symptoms of other atypical parkinsonian syndromes may also respond to medications used to treat idiopathic PD⁵. The changes in clinical exam over 36 months serves as “standard of truth (SOT) to determine a final clinical diagnosis of PD, has potential for error but it serves as a practical standard for this type of clinical trial. Autopsy results would serve as a true SOT, but this is not practical in early PD trials. The availability of 3 year data may improve on the level of diagnostic accuracy but it seems unlikely that this would result in change in diagnosis for a significant number of patients followed for 36 months.

In the case of DLB, elapsed time alone will not definitively establish a diagnosis of DLB disease. The application of consensus clinical criteria and over a 36 month period is also not definitive³. The diagnosis of “Probable DLB” may be confounded by the diagnosis of dementia associated with PD, which appears to be clinically distinct for DLB. Finally, studies using neuropathological criteria for classifying dementia acknowledge there may be overlapping pathology of DLB and Alzheimer’s dementia. In this reviewer’s opinion, clinical means alone should not serve as a gold standard to confirm an imaging diagnosis of DLB.

Question 2b

Please provide a general opinion regarding the strength of the clinical and supportive data in the NDA and as feasible, in the preparation for an advisory committee.

Clinical development Program

GE Healthcare has completed a total of 8 European clinical studies on DaTSCAN: one Phase 1 (CY95.FP.I), two Phase 2 (CY96.FP.II and PDT02005), four Phase 3 (DP008-003, PDT03004 [aka PDT304], PDT301, PDT03007) and one Phase 4 (PDT408). Of these studies, three have been deemed principal to support US registration of DaTSCAN_ for the proposed indication, namely DP008-003, PDT03004 (aka PDT304) and PDT301, with the addition of data to be provided from an investigator-initiated imaging-clinicopathological correlation study [Walker et al. 2007] in patients with along with a literature summary. Collectively, 942 subjects were dosed with DaTSCAN in the clinical

development program. There is also an ongoing Phase 4 trial (PDT408), which has enrolled 174 of 250 planned subjects as of 26 September 2008.

Best Available Copy

Tabular Listing of Supporting Clinical Trials

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT02005 (continued)		profile in subjects, following a single intravenous (i.v) injection of DaTSCAN™.						
Efficacy and Safety	DP008-003 US	[5.3.5.1]	Revised for US: Primary: Sensitivity and specificity for detecting or excluding a SDD. Secondary: Inter-reader agreement	Phase 3. Multicenter. Comparator-group. Open-label. Non-controlled. Non-randomized. No control.	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	224	Healthy subjects (35) Parkinsonian syndrome patients (160) Essential tremor patients (29)	1 dose	Complete; full
Efficacy and Safety	DP008-003 EU	[5.3.5.1]	Primary: To determine the sensitivity and specificity of striatal uptake of [¹²³ I]FP-CIT (DaTSCAN™) in patients with a clinical diagnosis of PD, MSA and PSP compared with ET. Secondary: To assess safety parameters (hematology, biochemistry and urinalysis, vital signs and ECG), and the adverse event profile in patients/volunteers following a single intravenous injection of [¹²³ I]FP-CIT (DaTSCAN™). To assess the striatal uptake of [¹²³ I]FP-CIT (DaTSCAN™) in healthy volunteers as a means to facilitate the calibration of imaging equipment at each study site.	Phase 3. Multicenter. Comparator-group. Open-label. Non-controlled. Non-randomized. No control.	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	224	Healthy subjects (35) Parkinsonian syndrome patients (160) Essential tremor patients (29)	1 dose	Complete; full
Efficacy and Safety	PDT03004 US (aka PDT304)	[5.3.5.1]	Revised for US: Primary: Sensitivity and specificity for detecting or excluding a SDD. Secondary: Inter-reader agreement	Phase 3. Multicenter. Open-label. Non-comparative. Non-randomized. Repeat administration. No control.	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	179	Parkinson's disease patients (71) Non-Parkinson's disease patients (31) Patients with no diagnosis (77)	3 single doses, 18 months apart	Complete; full
Efficacy and Safety	PDT03004 EU (aka PDT304)	[5.3.5.1]	Primary: To determine the predictive value of DaTSCAN™ SPECT to differentiate between subjects with early features of Parkinsonism, other causes of tremor (mainly ET), and healthy volunteers.	Phase 3. Multicenter. Open-label. Non-comparative. Non-randomized. Repeat	DaTSCAN™; single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	179	Parkinson's disease patients (71) Non-Parkinson's disease patients (31) Patients with no diagnosis (77)	3 single doses, 18 months apart	Complete; full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT03004 EU (aka PDT304) (continued)		Secondary: To determine if changes in DaTSCAN™ SPECT are representative of the progression in clinical symptomatology over 36 months. To assess safety parameters and the adverse event profile in subjects following a single intravenous injection of DaTSCAN™.	No control.					
Efficacy and Safety	PDT03007	[5.3.5.1]	Primary: To investigate the change in the uptake of DaTSCAN™ after two years, in healthy volunteers and subjects with Parkinsonian Syndrome and essential tremor, by SPECT imaging. Secondary: To assess the safety parameters (haematology, biochemistry and urinalysis, vital signs and ECG), and the adverse event profile in subjects following a single intravenous (i.v) injection of DaTSCAN™.	Phase 3. Multi-center. Open-label. Non-randomized. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	31	Healthy subjects (8) Parkinsonian syndrome patients (20) Essential tremor patients (3)		Complete, full
Efficacy and Safety	PDT301 US	[5.3.5.1]	Revised for US: Primary: Sensitivity and specificity for detecting or excluding a SDD. Secondary: Inter-reader agreement	Phase 3. Multi-center. Open-label. Non-randomized. Single-dose. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	326	Dementia patients (326)	1 dose	Complete, full
Efficacy and Safety	PDT301 EU	[5.3.5.1]	Primary: 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 of an independent CP used as the standard of truth. Secondary: To determine the accuracy, positive predictive value, and negative predictive value of DaTSCAN™ SPECT visual assessment findings when compared to the clinical diagnosis (i.e., probable DLB/ non-DLB) of the CP as the SOT. To compare the results of semi-	Phase 3. Multi-center. Open-label. Non-randomized. Single-dose. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	326	Dementia patients (326)	1 dose	Complete, full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT301 EU (continued)		quantitative analysis of the striatal uptake ratios of DaTSCAN™ SPECT images between probable, possible, and non-DLB in specific regions of interest (i.e., striatum, caudate, and putamen in both hemispheres). To assess the impact of DaTSCAN™ SPECT visual assessment findings on the on-site investigator's ability and level of confidence to establish a diagnosis and to make a management decision. To assess the proportions of abnormal DaTSCAN™ SPECT visual assessment findings in relation to the groups of 'probable DLB', 'possible DLB', and 'non-DLB'. To review the efficacy analysis via the re-assessment of the clinical diagnosis established by the CP after a 12-month follow-up period. To confirm the safety profile of a single i.v. injection of DaTSCAN™ in the subject population.						
Efficacy and Safety	PDT408 US	[5.3.5.1]	Revised for US: Primary: Impact of DaTSCAN™ image assessments on patient diagnoses, confidence that patient had PS, and planned management.	Phase 3b/4. Multi-center. Open-label. Non-randomized. Non-comparative. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	120	Parkinsonian syndrome patients (120)	1 dose or, 2 doses, 24 months apart	Complete, full
Efficacy and Safety	PDT408 EU	[5.3.5.1]	Primary: To assess the striatal uptake of DaTSCAN™ SPECT in subjects with clinically uncertain PS to help in the differentiation between 'PS' (i.e. associated with dopaminergic deficit, including idiopathic PS, MSA, PSP or other true Parkinsonian disorders) and 'non-PS' (i.e. other movement disorders). Secondary: To assess the ability of DaTSCAN™ SPECT imaging to increase diagnostic confidence in PS.	Phase 3b/4. Multi-center. Open-label. Non-randomized. Non-comparative. No control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	120	Parkinsonian syndrome patients (120)	1 dose or, 2 doses, 24 months apart	Complete, full

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy	GE-001-Walker EU	[5.3.5.1]	<p>Objectives of the first, cross-sectional stage of the study: To compare DaTSCAN™ radio-uptake ratios in the caudate nucleus, anterior and posterior putamen as determined by semi-quantitative, ROI based image assessment in patients with the clinical diagnoses of DLB, PD and AD and in controls. The baseline clinical diagnosis as established by an old age psychiatrist following a comprehensive clinical, neurological and neuropsychiatric examination and based on internationally accepted diagnostic criteria served as a reference standard for the cross-sectional study phase.</p> <p>Objectives of the second, longitudinal stage of the study: To determine the sensitivity and specificity of the ROI-based semi-quantitative analysis of DaTSCAN™ radio-uptake ratios in the caudate nucleus, anterior and posterior putamen when compared to the neuropathological diagnosis at autopsy as the SOT. To determine the sensitivity and specificity of the visual assessment of the DaTSCAN™ images analyzed by 3 readers (in consensus who were blinded to all clinical information) when compared to the neuropathological diagnosis at autopsy as the SOT. To determine the sensitivity and specificity of the clinical diagnosis (reference standard of the cross-sectional study phase) when compared to the neuropathological diagnosis at autopsy as the SOT.</p>	Investigator-initiated. Proof-of-concept. Open-label. Cross-sectional. Longitudinal.	DaTSCAN™, single injection containing approximately 150-185 MBq (4-5 mCi); intravenous injection	80	Alzheimer's disease patients (17) Parkinson's disease patients (19) Dementia with Lewy bodies patients (27) Cortico-basal degeneration patients (1) Healthy subjects (16)	1 dose	Ongoing; interim

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	PDT408 EU (continued)		<p>To identify possible cases where DaTSCAN™ SPECT imaging had impact on patient management. To assess the adverse event profile in subjects following a single intravenous injection of DaTSCAN™.</p>						
Efficacy	PDT409		<p>Primary: To assess the influence of DaTSCAN™ imaging on the clinical management of subjects with clinically uncertain parkinsonism. Secondary: To assess the influence of DaTSCAN™ imaging on the diagnosis of subjects with clinically uncertain parkinsonism. To assess changes in diagnostic confidence after DaTSCAN™ imaging. To describe healthcare resource use (HRU) from baseline to follow up. To explore the influence of DaTSCAN™ imaging on the Quality of Life (QoL) from baseline to follow up.</p>	Phase 4. Multi-center. Open-label. Randomized. Comparative. Non-dosed control.	DaTSCAN™, single injection containing approximately 111-185 MBq (3-5 mCi); intravenous injection	250 (planned)	Clinically uncertain Parkinsonism patients.	1 dose	Ongoing; none
Efficacy	GE-001-Walker US	[5.3.5.1]	<p>Revised for US: To determine the sensitivity and specificity of: The visual assessment of DaTSCAN™ images based on the consensus of three readers who were blinded to all clinical information compared to the neuropathological diagnosis at autopsy (standard of truth in the longitudinal phase) The baseline clinical diagnosis (the SOT of the cross-sectional phase of the study) compared to the neuropathological diagnosis at autopsy (the SOT in the longitudinal phase) ROI-based semi-quantitative analysis of DaTSCAN™ radioactivity uptake ratios in each striatum (specifically, the caudate nucleus and the anterior and posterior putamen) compared to the neuropathological diagnosis at autopsy (the SOT in the longitudinal phase)</p>	Investigator-initiated. Proof-of-concept. Open-label. Cross-sectional. Longitudinal.	DaTSCAN™, single injection containing approximately 150-185 MBq (4-5 mCi); intravenous injection	80	Alzheimer's disease patients (17) Parkinson's disease patients (19) Dementia with Lewy bodies patients (27) Cortico-basal degeneration patients (1) Healthy subjects (16)	1 dose	Ongoing; interim

PD Versus Non-PD Diagnosis (Reviewer Comment)

The clinical trials have a primary endpoint of sensitivity and specificity. The design is open label, using blinded raters, on site and blinded central readers for the SPECT images. Clinical rating was conducted by blinded movement disorders experts viewing videotaped exams supplemented with some clinical data.

Summary of results of the primary endpoint of pivotal studies in patients with early PD versus non-PD indicate a low sensitivity. This is due to patients with normal SPECT Scans in patients who have early PD based on SOT clinical exam. The specificity of detecting SDD has a median value of 97% at baseline and at 36 months. At baseline when most patients would present for diagnosis the specificity would aid in distinguishing PD from other non-PD disorders.

Summary of Sensitivity and Specificity by Clinical Diagnosis—Blind Image Reads (Sponsor’s text) Pooled Analysis

Sensitivity and specificity were summarized from for all 4 principal studies. Because no blinded read was conducted in study PDT408, the data from that study are not included in pooled analyses of blinded read data. For detecting a symptomatic dopaminergic deficit in the pooled ITD population for subjects with symptoms of a *movement disorder* (where the clinical context would allow differentiation between SDD-related conditions such as PS/PD and non-SDD related conditions such as ET), the sensitivity of individual blind readers at baseline ranged from a low of 75.0% to a high of 96.8%, and the specificity ranged from 80.6% to 96.8%. Results were comparable at 12, 18, and 36 months for those studies that included these time points. The mean results for sensitivity across all readers were 91.1% (95% CI = 89.2, 92.8) at baseline, 78.9% (72.8, 84.2) at month 18, and 76.6% (70.1, 82.3) at month 36. For specificity, the mean results for all readers were 92.3% (89.3, 94.7) at baseline, 95.7% (89.2, 98.8) at month 18, and 96.7% (90.6, 99.3) at month 36.

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Table 13 Summary of Sensitivity and Specificity by Expert Clinical Diagnosis—Individual Blind Reads—ITD Population All Subjects (N = 726)

Response	Expert Clinical Diagnosis (SOT)					
	Parkinsonian Syndrome (PS; SDD)		Dementia with Lewy Bodies (DLB; SDD)		Total	
	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)	Sensitivity (%, 95% CI)	Specificity (%, 95% CI)
Study DP008-003						
Reader A	93.0% (87.9, 96.5)	93.5% (84.3, 98.2)				
Reader B	96.8% (92.8, 99.0)	80.6% (68.6, 89.6)				
Reader C	96.2% (91.9, 98.6)	91.9% (82.2, 97.3)				
Reader D	92.4% (87.1, 96.0)	96.8% (88.8, 99.6)				
Reader E	94.3% (89.5, 97.4)	91.9% (82.2, 97.3)				
Study PDT03004 (aka PDT304) - Baseline						
Reader A	77.5% (66.0, 86.5)	96.8% (83.3, 99.9)				
Reader B	77.9% (66.2, 87.1)	96.8% (83.3, 99.9)				
Reader C	78.6% (67.1, 87.5)	96.8% (83.3, 99.9)				
Study PDT03004 (aka PDT304) - Month 18						
Reader A	77.5% (66.0, 86.5)	96.7% (82.8, 99.9)				
Reader B	77.5% (66.0, 86.5)	93.5% (78.6, 99.2)				
Reader C	81.7% (70.7, 89.9)	96.8% (83.3, 99.9)				
Study PDT03004 (aka PDT304) - Month 36						
Reader A	75.0% (63.0, 84.7)	96.7% (82.8, 99.9)				
Reader B	76.9% (64.8, 86.5)	96.7% (82.8, 99.9)				
Reader C	77.9% (66.2, 87.1)	96.7% (82.8, 99.9)				
Study PDT301 - Baseline						
Reader A			79.7% (69.2, 88.0)	91.2% (85.2, 95.4)		
Reader B			75.3% (64.2, 84.4)	88.5% (82.0, 93.3)		
Reader C			80.2% (69.9, 88.3)	90.5% (84.3, 94.9)		

Reviewer Comment

The sensitivity of DaTSCAN appears to offer little or no advantage over clinical diagnosis. The lower bounds of the C.I. for specificity appear to be the same as the estimate of 89% of diagnostic accuracy using clinical criteria alone.

DLB Versus Non-DLB Dementia (Reviewer Comment)

The benefit of DaTSCAN imaging in distinguishing DLB and Alzheimer’s dementia appears to be more limited. Both sensitivity and specificity appear to offer little advantage over clinical diagnosis. The Walker study is an investigated initiated supporting study that incorporated autopsy results as the final truth standard in making the diagnosis of DLB versus non-DLB (Alzheimer’s dementia). There were 22 cases with autopsy results reported along with the DaTSCAN results. In 8 cases (see the table below), the clinical and DaTSCAN diagnosis disagreed. In 4 of the cases (highlighted in yellow), the post-mortem findings proved the DaTSCAN diagnosis were wrong. In another 4 cases, the DaTSCAN and postmortem diagnosis proved the clinical diagnosis was incorrect (red boxed). The net result indicates DaTSCAN imaging was not superior in making the correct diagnosis on DLB or non-DLB when compared to the autopsy evidence in cases where the clinical diagnosis may be uncertain.

Table 5 Diagnostic Results by Subject

Case No	Gender	Age at DaTSCAN™ Imaging	Post-Mortem Diagnosis	Baseline Clinical Diagnosis	Baseline Clinical Diagnosis Classification	Visual DaTSCAN™ Image Assessment	Visual DaTSCAN™ Image Classification
1	Male	78	DLB	AD	Non-DLB	Abnormal	DLB
2	Male	82	DLB	DLB	DLB	Abnormal	DLB
3	Male	77	DLB	DLB	DLB	Normal	Non-DLB
4	Female	82	DLB	DLB	DLB	Abnormal	DLB
5	Female	58	DLB	CBD	Non-DLB	Abnormal	DLB
6	Female	84	DLB	DLB	DLB	Abnormal	DLB
7	Female	82	DLB	DLB	DLB	Abnormal	DLB
8	Female	69	DLB	DLB	DLB	Abnormal	DLB
9	Female	77	Non-DLB	AD	Non-DLB	Normal	Non-DLB
10	Male	77	Non-DLB	AD	Non-DLB	Normal	Non-DLB
11	Female	76	Non-DLB	DLB	DLB	Abnormal	DLB
12	Male	76	Non-DLB	DLB	DLB	Normal	Non-DLB
13	Male	85	Non-DLB	DLB	DLB	Normal	Non-DLB
14	Male	67	Non-DLB	DLB	DLB	Normal	Non-DLB
15	Male	95	Non-DLB	AD	Non-DLB	Normal	Non-DLB
16	Male	84	Non-DLB	AD	Non-DLB	Normal	Non-DLB
17	Male	68	Non-DLB	DLB	DLB	Abnormal	DLB
18	Male	63	Non-DLB	DLB	DLB	Normal	Non-DLB
19	Male	81	Non-DLB	DLB	DLB	Normal	Non-DLB
20	Female	85	Non-DLB	AD	Non-DLB	Normal	Non-DLB
21	Female	74	Non-DLB	AD	Non-DLB	Normal	Non-DLB
22	Male	86	DLB	DLB	DLB	Normal	Non-DLB

AD = Alzheimer’s disease; CBD =cortico-basal degeneration; DLB = dementia with Lewy bodies.
 REF: Section 14.2, Table [4]

Analysis of Pooled Data (Sponsor's text)

For detecting a SDD in the pooled intention to diagnose (ITD) population for subjects with symptoms of *dementia* (where the clinical context would allow differentiation between SDD-related conditions such as DLB and Parkinson's disease with dementia [PDD] and non-SDD related conditions such as AD and Vascular dementia (VaD), the sensitivity of individual blind readers at baseline ranged from a low of 75.3% to a high of 82.3%, and the specificity ranged from 88.5% to 91.2%. The results at month 12 were comparable. The mean results across all readers for diagnosis of DLB were, at baseline, 78.5% (72.7, 83.5) for sensitivity and 90.1% (86.8, 92.8) for specificity. At month 12, the mean results for all readers were 78.5% (72.7, 83.5) for sensitivity and 92.8% (89.6, 95.2) for specificity. The submission did not appear to contain data suggesting DaTSCAN could distinguish dementia associated with PD from other causes for dementia.

Reviewer's Comment

The progressive asymmetric loss of pigmented neurons containing DAT in the striatum is a key pathological feature of Idiopathic Parkinson's disease. In Atypical Parkinsonian Syndromes (PS), dementia with Lewy bodies (DLB), and other related diseases, dopamine loss in the striatum may not be as prominent and more evenly distributed, making it more difficult to distinguish between these disorders using DAT imaging. DaTSCAN images the Dopamine Transporter (DAT) molecule in pre-synaptic dopaminergic nerve terminals. A similar DAT SPECT imaging agent was incorporated into U.S. Parkinson's disease clinical drug trials to explore their potential for detecting early PD and their potential to act as a marker for disease progression. The most often studied DAT SPECT agent studies in U.S. PD trials is 2 beta-carboxymethoxy-3 beta(4-iodophenyl) tropane (beta-CIT). One recognized flaw associated with DAT SPECT (beta-CIT) imaging is a potential confounding effect caused by co-administration of dopaminergic drugs given to treat the symptoms of Parkinson's disease. A frequently cited example of this flaw associated with beta-CIT SPECT is discussed in the results of The ELLDOPA Study (Fahn et al. NEJM 351:249, 2004; PMID: 15590952)⁵. Patients in the ELLDOPA trial treated with carbidopa/levodopa (CD/LD) appeared to have undergone significant dopaminergic neuronal loss observed on beta-CIT SPECT scanning compared to the placebo treated group. However, clinically these patients performed better than placebo treated patients. In addition, some early PD patients had normal beta-CIT SPECT scans initially but were later determined to have PD by clinical observation over time (the sponsor's diagnostic gold standard used in DaTSCAN trials). Once patients in the ELLDOPA trial were washed out from treatment with CD/LD (off levodopa for 2 weeks), they appeared to maintain a symptomatic benefit over the placebo treated group. The clinical observations suggested that levodopa may have a disease modifying benefit contrary to the results of beta-CIT scans suggesting their striatal neuronal loss had progressed. One of the possible explanations is that treatment with levodopa may cause down-regulation of DAT⁴. The finding casts doubt on the notion that DAT imaging is reliable in patients treated with levodopa and potentially other dopaminergic medications. The sponsor counters this argument by stating that drugs affecting the dopamine transporter would be evenly distributed and the effect would not impact the DaTSCAN interpretation. Although, this may be true, it could potentially be a problem in patients who might receive DaTSCAN to evaluate possible ET, Alzheimer's disease and DLB, where a diffuse reduction in DAT imaging may be the typical pattern of abnormality.

Answer To Question 2b

The sensitivity of DaTSCAN in some early PD patients of DaTSCAN is limited. The specificity in a select group of patients, who are examined carefully and the differential diagnosis is limited to PD versus ET. DaTSCAN appears to be acceptable for providing additional information to distinguish most, but not all patients with PD. The sponsor's experience in differentiating idiopathic Parkinson's disease from multiple system atrophy (MSA) progressive supranuclear palsy (PSP) and psychogenic parkinsonism is too limited clearly determine that DaTSCAN can distinguish between these disorders and PD in their early stages. DaTSCAN imaging becomes unnecessary, once the symptoms of these atypical parkinsonian syndromes declare themselves clinically. When autopsy data is used as the gold standard of evidence, the data does not support the notion that DaTSCAN imaging is superior to clinical diagnosis, for distinguishing DLB from non-DLB.

The sponsor should supply evidence that anti-parkinsonian drugs (at least levodopa and dopamine agonists) do not affect DaTSCAN imaging or that adjustments can compensate for these changes.

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