CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200655Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Class 2 Resubmission NDA
Application Number(s)	200655
Priority or Standard	Class 2 Resubmission Review
Submit Date(s)	4/10/2019 Amendments: 5/08/19,7/10/19,7/22/19, 9/11/19,9/30/19
Received Date(s)	4/10/2019
PDUFA Goal Date	10/10/2019
Division/Office	DMIP/ ODE IV
Review Completion Date	10/10/2019
Established/Proper Name	Fluorodopa F 18
(Proposed) Trade Name	None
Pharmacologic Class	Radioactive Diagnostic Agent for Positron Emission Tomography
Code name	5020600
Applicant	The Feinstein Institutes for Medical Research
Dosage form	Injection
Applicant proposed Dosing Regimen	(b) (4) 5.0 mCi intravenous injection, single administration
Applicant Proposed Indication(s)/Population(s)	Used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected Parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	32798002 Parkinsonism (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Fluorodopa F 18 Injection is a radioactive diagnostic agent indicated for use in positron emission tomography (PET) to visualize dopaminergic nerve terminals in the striatum for the evaluation of adult patients with suspected Parkinsonian syndromes (PS). Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.
Recommended SNOMED CT Indication Disease Term for each Indication	32798002 Parkinsonism (disorder)
Recommended Dosing Regimen	5 mCi intravenous infusion over 1 minute, single administration

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality

OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Fluorodopa F 18 injection (^{18}F-FDOPA) is a PET radiopharmaceutical that crosses the blood-brain barrier and is converted to F-18 fluorodopamine by aromatic amino acid decarboxylase (AAAD) in the striatum. The resultant F-18 fluorodopamine is then stored in the vesicles of the striatal terminals of dopaminergic neurons.

^{18}F-FDOPA is proposed as a Positron Emission Tomography (PET) agent for use in the evaluation of patients with suspected Parkinsonian syndromes (PS). The Parkinsonian symptoms of PS are caused by degeneration of dopaminergic neurons in the brain. Due to the infeasibility of histopathological confirmation of this process, diagnosis of PS relies on clinical evaluation. However, significant overlap in clinical features between PS and a host of non-Parkinsonian syndromes (non-PS) can lead to uncertainty in clinical diagnosis. In contradistinction to PS, the Parkinsonian symptoms of non-PS are not due to degeneration of dopaminergic neurons. Diagnostic distinction between PS and non-PS is clinically important because of differences in patient management.

The mechanism of ^{18}F-FDOPA allows it to act as a marker of dopaminergic neurodegeneration when imaged by PET. In the setting of PS, the uptake and storage of ^{18}F-FDOPA in the striatum will be reduced. The resultant PET imaging will show decreased signal unilaterally or bilaterally in the putamen and possibly the caudate. In the setting of non-PS, ^{18}F-FDOPA PET imaging will show normal signal in the caudate and putamen bilaterally. Of note, even patients at the onset of PS often have substantial degeneration of dopaminergic neurons in the brain. PET imaging with ^{18}F-FDOPA is thus proposed as an adjunct to other clinical evaluation in the assessment of patients with suspected PS.

^{18}F-FDOPA was one of the unapproved PET drugs in clinical use pending the development by FDA of cGMP regulations governing the production of PET drugs. In 2000, FDA review of the published literature concluded that ^{18}F-FDOPA "marks the dopaminergic system and may be used as a biomarker". Since the establishment of FDA cGMP regulation of PET drugs, ^{18}F-FDOPA has continued to be studied in the US under INDs and has also been used under expanded access INDs.

^{18}F-FDOPA PET was approved in France in 2010 followed by several other countries in the European Union. ^{18}F-FDOPA approval in France and other EU countries was based solely on published clinical studies, particularly the study by Eshuis et al. (2009)[1] discussed in Section 8.1.2.

[1] Eshuis et al. Direct comparison of FP-CIT SPECT and F-DOPA PET in patients with Parkinson's disease and healthy controls. Eur J Nucl Med Mol Imaging (2009) 36:454–462

1.2. Conclusions on the Substantial Evidence of Effectiveness

This resubmission addressed all deficiencies identified in previous review cycles. The first FDA review in 2012 concluded that the submitted retrospective chart review and published literature were inadequate to support a 505(b)(2) application, and the FDA recommended that the Applicant conduct a prospective clinical study. In response, the Applicant prospectively conducted Study #17. However, this study was found to have the following major deficiencies that lead to a complete response in a review cycle ending in 2016:

- An incomplete reference standard since a substantial number of patients did not complete clinical follow-up at the pre-specified minimum time interval of 1-year.
- Potential bias in generating the clinical reference standard since the image interpretation results of ^{18}F-FDOPA PET were known to the reference standard clinicians prior to their determination of follow-up diagnosis.

Study #18 from the Applicant's current submission adequately addressed these prior deficiencies. In this prospective trial, a total of 56 patients with possible PS out of the 68 enrolled completed the pre-specified requirement of at least 6 months of clinical follow-up. Furthermore, the reference standard was established by a movement disorder specialist who remained blinded to ^{18}F-FDOPA PET results. Thus, the clinical reference standard used in Study #18 was found to be satisfactory by the review team. Visual interpretation of ^{18}F-FDOPA PET imaging with a binary reading method demonstrated a high negative percent agreement (with a 95% confidence interval as low as 61% and as high as 99%) relative to the clinical reference standard in all 3 blinded, independent readers but lower positive percent agreement (with a 95% confidence interval as low as 31% and as high as 87%) among these same 3 readers. The review team concluded that these results support the effectiveness of ^{18}F-FDOPA PET for use as an adjunct to other diagnostic evaluations in patients with suspected PS.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Parkinsonism is a general clinical term used to describe any combination of bradykinesia, rest tremor, rigidity, and postural instability. Movement disorders featuring Parkinsonism can be divided into those that are associated with degeneration of dopaminergic neurons (referred to as Parkinsonian syndromes (PS)) and those that are not (referred to as non-Parkinsonian syndromes (non-PS)).

PS includes progressive and serious disorders such as Parkinson's disease, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal degeneration (CBD). Non-PS includes essential tremor, dystonic tremor, psychogenic Parkinsonism, drug-induced Parkinsonism, vascular Parkinsonism, and other conditions.

Diagnostic distinction between PS and non-PS is clinically important because of respective differences in patient management. Due to the infeasibility of histopathological confirmation, differentiation of patients with PS from those with non-PS continues to be based on clinical evaluation. Unfortunately, overlap in clinical features between PS and non-PS often makes distinguishing between them challenging. Strategies to address such diagnostic uncertainty are limited and not ideal, such as trial of levodopa therapy and continued long-term clinical follow-up.

^{18}F-FDOPA PET provides an adjunctive non-invasive approach to evaluation of this patient population. As a radiolabeled analog of levodopa, ^{18}F-FDOPA uptake in the striatum can be imaged by PET to assess dopaminergic neurons. In the setting of PS, ^{18}F-FDOPA PET imaging should show decreased striatal signal. In the setting of non-PS, ^{18}F-FDOPA should show normal striatal signal.

In this resubmission, the Applicant provided results from an adequate and well-controlled prospective trial (Study #18) that addressed deficiencies noted by the FDA in prior review cycles. A clinical reference standard was established in 56 patients with suspected PS through at least 6 months of clinical follow-up by a movement disorder specialist who remained blinded to ^{18}F-FDOPA PET results. Visual interpretation of ^{18}F-FDOPA PET imaging with a binary reading method demonstrated a high negative percent agreement (with a 95% confidence interval as low as 61% and as high as 99%) in all 3 blinded, independent readers relative to the clinical reference standard but lower positive percent agreement (with a 95% confidence interval as low as 31% and as high as 87%) among these same 3 readers. The review team concluded that these results adequately support the effectiveness of ^{18}F-FDOPA PET for use an adjunct to other diagnostic evaluations in patients with suspected PS.

Safety of ^{18}F-FDOPA is supported by extensive clinical experience with much higher and long-term dosing of the closely related therapeutic drug, levodopa. Additionally, review of safety data collected from 121 patients exposed to ^{18}F-FDOPA in Study #17 and Study #18 raises no concerns. Patient radiation exposure from ^{18}F-FDOPA PET (estimated effective dose of 5.6 mSv) is similar to that of other commonly used diagnostic radiopharmaceuticals. The review team concluded that risks of ^{18}F-FDOPA are low and further mitigated by its recommended single dosage.

The low risks of ^{18}F-FDOPA PET are outweighed by its benefit as an adjunct to other diagnostic evaluations in patients with suspected PS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Movement disorders featuring Parkinsonism that is caused by dopaminergic degeneration (referred to as Parkinsonian syndromes (PS)) include: Idiopathic Parkinson's disease (IPD) Progressive supranuclear palsy (PSP) Multiple system atrophy (MSA) Corticobasal degeneration (CBD) Movement disorders featuring Parkinsonism that is not caused by dopaminergic degeneration (referred to as non-Parkinsonian syndromes (non-PS)) include: Essential tremor (ET) Isolated resting tremor Dystonic tremor Drug-induced Parkinsonism Vascular Parkinsonism Psychogenic Parkinsonism	PS includes several serious, progressive disorders that may respond to therapy directed at dopaminergic degeneration, such as oral levodopa. Diagnostic distinction between PS and non-PS is clinically important because of respective differences in patient management. Differentiation of patients with PS from patients with non-PS is currently based on clinical evaluation. Clinical differentiation of PS and non-PS is often difficult due to shared signs and symptoms between these groups of disorders.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	DaTscan is a SPECT imaging agent approved to help differentiate essential tremor (non-PS) from tremor due to PS. Brain CT and MRI contribute little to diagnosis or differentiation of PS and non-PS beyond potentially excluding other pathology. Other diagnostic imaging options for differentiating PS and non-PS are investigational at this time.	Other than DaTscan, no approved imaging tests typically contribute to traditional clinical evaluation of patients with suspected PS. DaTscan is for use with SPECT while ^{18}F-FDOPA is for use with PET. PET is a higher resolution imaging technique than SPECT, allowing improved image appearance and reduced scan time. ^{18}F-FDOPA has a different molecular mechanism of action than DaTscan.
Benefit	In Study #18, ^{18}F-FDOPA PET demonstrated high negative percent agreement but low positive percent agreement with a reference standard of PS or non-PS that was established by clinical follow-up. Similar results were demonstrated in the clinically relevant subgroup of patients who had symptoms for 2 years or less.	Study #18 adequately addressed deficiencies noted in the previous complete response. ^{18}F-FDOPA PET can be used as an adjunct to other diagnostic evaluations for patients with suspected PS.
Risk and Risk Management	^{18}F-FDOPA safety is supported by extensive clinical experience with much higher and long-term dosing of the closely related therapeutic drug, levodopa. Available safety data from Study #17 and Study #18 demonstrate a benign safety profile for ^{18}F-FDOPA. Patient radiation exposure from ^{18}F-FDOPA PET (estimated effective dose of 5.6 mSv) is similar to that of other diagnostic radiopharmaceuticals.	Potential risks of ^{18}F-FDOPA use are low. ^{18}F-FDOPA is intended for single use thus further limiting risks from radiation and drug exposure.

2. Therapeutic Context

2.1. Analysis of Condition

Parkinsonism is a general clinical term used to describe any combination of bradykinesia, rest tremor, rigidity, and postural instability. Movement disorders featuring Parkinsonism can be divided into those that are associated with degeneration of dopaminergic neurons and those that are not. In this review, the former group of disorders in which Parkinsonism is caused by dopaminergic degeneration will be referred to as Parkinsonian syndromes (PS) and the latter group in which Parkinsonism is not caused by degeneration of dopaminergic neurons will be termed non-Parkinsonian syndromes (non-PS).

PS includes Idiopathic Parkinson's disease (IPD) and Atypical Parkinson's disease (APD). APD can be further subdivided into multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and other disorders. These diseases are progressive and serious, often resulting in significant patient disability. In the setting of PS, ^{18}F-FDOPA PET imaging should show decreased striatal signal, as referred to in this review as a positive scan.

Non-PS includes essential tremor, dystonic tremor, psychogenic Parkinsonism, drug-induced Parkinsonism, vascular Parkinsonism, and other conditions. In the setting of non-PS, ^{18}F-FDOPA should show normal striatal signal, as referred to in this review as a negative scan.

Diagnostic distinction between PS and non-PS is clinically important because of respective differences in patient management. Patients with PS, particularly IPD, may benefit from therapies directed at dopaminergic degeneration, such as oral levodopa. Conversely, levodopa treatment response would typically not be expected in patients with non-PS.

Although definitive distinction of PS and non-PS could be made histopathologically, obtaining brain tissue for this purpose is impractical. Thus, differentiation of patients with PS from those with non-PS continues to be based on clinical evaluation. However, overlap in clinical features between PS and non-PS often makes distinguishing between them challenging. Strategies to address such diagnostic uncertainty are limited and not ideal, such as trial levodopa therapy and continued long-term clinical follow-up.

2.2. Analysis of Current Treatment Options

DaTscan (Ioflupane I 123 Injection, I-123 FP-CIT) is FDA approved for very similar indications to those currently proposed for ^{18}F-FDOPA:

> DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations.

While both DaTscan and ^{18}F-FDOPA are targeted to the terminals of dopaminergic neurons in the striatum, their precise mechanisms of localization differ. DaTscan binds directly to the dopamine transporter (DaT) while ^{18}F-FDOPA is a levodopa analog. The I-123 radiolabel of DaTscan makes it compatible with SPECT imaging. PET has higher spatial resolution than SPECT and is compatible with the F-18 radiolabel of ^{18}F-FDOPA.

Although numerous CT and MRI contrast agents are approved for brain imaging and are used extensively for this purpose, CT and MRI have very limited utility for the imaging and differentiation of PS and non-PS. Some studies suggest a possible role for imaging glucose metabolism with ^{18}F-FDG PET in the setting of Parkinson’s disease, although this use currently remains investigational.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The first New Drug Application (NDA 200655) for ^{18}F-FDOPA was submitted to FDA on October 29, 2009. This submission was based on peer-reviewed publications. FDA refused to file the application on the basis that the submission did not contain adequate information to allow a substantial review.

The second New Drug Application (NDA 200655) for ^{18}F-FDOPA was submitted to FDA on October 23, 2012. The submitted clinical data was based on a retrospective chart review of 185 patients at the Applicant's institution. FDA review found the submitted clinical data to be inadequate to support the proposed indication and issued a Complete Response (CR) letter dated 10/22/2013. The FDA recommended that the Applicant conduct a prospective clinical study to support the proposed indication.

The Applicant re-submitted the NDA on December 15, 2015. The submission included a prospective clinical study (Study #17) of 45 patients that was conducted under an expanded access IND at the Applicant's own institution. FDA review found this study to be poorly conducted with a substantial percentage of patients lacking the prespecified one-year clinical follow-up as the standard of reference. In addition, FDA review noted that the PET image interpretations were known to the physicians providing clinical follow-up prior to their determination of the clinical diagnosis, leading to potential bias in the resultant reference standard. FDA again issued a CR letter dated 09/15/2016.

The current resubmission is a response to the most recent FDA CR letter dated 09/15/2016. This resubmission is based on a new prospective clinical study (Study #18) that was developed with FDA guidance and completed at the Applicant's own institution.

3.2. Foreign Regulatory Actions and Marketing History

^{18}F-FDOPA PET was approved in France in 2010 followed by several other countries in the European Union. Fluorodopa F 18 PET approval in France and other EU countries was based solely on clinical studies in the published literature. These clinical studies were not conducted by the pharmaceutical companies who market the drug.

European tradenames for ^{18}F-FDOPA are Dopacis and IASOdopa. Approved indications include uses in neurology and oncology. The neurology indication for Dopacis according to the product's labeling is as follows:

> PET with fluorodopa (18F) is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain parkinsonian syndromes. It can be used to differentiate essential tremor from parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system (Parkinson disease (PD), multisystem atrophy and progressive supranuclear palsy).

PET with fluorodopa (18F), on its own, is unable to discriminate between different parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system. It is also unable to discriminate between PD with and without tremor.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Applicant-investigator inspection of The Feinstein Institutes for Medical Research was performed as a data audit for NDA 200655 during the first review cycle in 2013. The inspections revealed that available records did not appear to meet the good clinical practice (GCP) standards for an NDA. A prospective study protocol and case report forms (CRFs) were not used and important study records (including source records) were not available for inspectional review. A Form 483 was issued for: (1) failure to prepare and maintain adequate case histories, and (2) inadequate investigational drug disposition records with respect to dates, quantity, and use by subjects.

During the subsequent review cycle of the resubmitted NDA in 2016, Study #17 was audited with GCP inspection of the Applicant-investigator site. No significant deficiencies were noted. The overall study conduct appeared GCP-compliant, including oversight of study conduct. All audited data were adequately verifiable against source records and case report forms. Given these recent satisfactory inspection findings at the same site where Study #18 was conducted, no audit was performed for the current resubmission.

5. Nonclinical Pharmacology/Toxicology Executive Summary

This NDA should be approved from a nonclinical perspective.

The Applicant did not conduct any nonclinical studies to support the application. The initial nonclinical submission for approval of "Fluorodopa F 18 Injection" was reviewed by Dr. Sally Hargus. Nonclinical recommended the approval of the NDA based upon:

- Structural similarities between ^{18}F-FDOPA and levodopa.
- The availability of extensive nonclinical and clinical databases on levodopa.
- The availability of a nonclinical pharmacology data on ^{18}F-FDOPA.
- The safety of ^{18}F-FDOPA demonstrated by historical use of levodopa for treatment of Parkinson's disease at prescribed doses of up to 2000 mg per day for chronic use (Carbidopa/Levodopa Monograph 2013), which is more than (b) (4)-fold the one-time intravenously-administered ^{18}F-FDOPA mass dose of (b) (4) mg or less.

Moreover, in 2000, FDA conducted a multidisciplinary review and evaluation of ^{18}F-FDOPA injection in preparation for a public meeting with the clinical PET community. Dr. Laniyonu[2] wrote the nonclinical portion of FDA review based on publicly available nonclinical information on ^{18}F-FDOPA and nonclinical and clinical literature on levodopa. Nonclinical reiterates the initial recommendation for the NDA application.[3] [4]

Recommendation

The application is recommended for approval from a nonclinical perspective.

[2] Non-Clinical Secondary Review dated June 18, 2013
[3] Non-Clinical Primary Review dated June 10, 2013
[4] Non-Clinical Primary Review dated April 13, 2016

6. Clinical Pharmacology Executive Summary

No new clinical pharmacology study was performed in this resubmission. The original submission was acceptable from a clinical pharmacology perspective and no postmarketing requirements or commitments were recommended.[5] [6]

Recommendations

This NDA is approvable from a clinical pharmacology perspective, provided the Applicant and the Agency reach an agreement on labeling language.

Table 1. Overall Clinical Pharmacology Recommendations

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The effectiveness of ^{18}F-FDOPA for the proposed indication is based on data from a single-center study (Study #18) that determined positive percent agreement and negative percent agreement with the clinical standard of reference.
General dosing instructions	Acceptable as the proposed IV dose of ^{18}F-FDOPA at 5 mCi is found safe and effective in clinical Study #18.

Post-Marketing Requirements and Commitments

None.

6.1. Summary of Clinical Pharmacology Assessment

6.1.1. Pharmacology and Clinical Pharmacokinetics

There are no new clinical pharmacology studies conducted as a part of this new submission. This re-submission contains only one additional clinical study, Study #18.

In this study,150 mg of carbidopa was administered to patients orally 60 minutes (approximately) prior to the administration of ^{18}F-FDOPA. The use of carbidopa may increase ^{18}F-FDOPA bioavailability to the brain by inhibiting peripheral decarboxylase activity and restricting peripheral ^{18}F-FDOPA metabolism.

The study dose was 5±10% mCi of ^{18}F-FDOPA, which is not significantly different than that used in the clinical study submitted in the original NDA (Study #15) and first CR resubmission (Study #17).

At about 70 minutes post injection patients were asked to void to remove radioactivity collected in the bladder. Patients were then positioned for scanning. Images were acquired as follows: a 9 second CT scan was initiated at about 79 minutes post injection followed by a 3D PET scan from 80 to 100 minutes.

[5] Clinical Pharmacology Primary Review dated June 13, 2013
[6] Clinical Pharmacology Primary Review dated April 14, 2016

For this clinical study, ^{18}F-FDOPA PET scans were interpreted by visual observation of the scan, based upon the appearance of the putamen and caudate in the striatum. In patients with PS, ^{18}F-FDOPA PET images are expected to reflect degeneration of dopaminergic neurons through a decrease in striatal signal, referred to in this review as a positive scan. In non-PS patients, ^{18}F-FDOPA PET is expected to show normal striatal signal, referred to in this review as a negative scan.

Three radiologists evaluated the PET images. High negative percent agreement (point estimate range of 83% to 91%) and lower positive percent agreement (point estimate range of 49% to 73%) were obtained, confirming that ^{18}F-FDOPA PET can be used as an adjunct to other diagnostic evaluations.

In addition, the Applicant conducted an analysis based on semi-quantitative measurements using striatal/occipital ratio (SOR) to assess correlation with visual PET scan results. (b) (4) This SOR quantification does not require any special software program. For Study 18, the SOR values were not used for the visual determination of the PET scan results. The PET image readers and the physician establishing the reference standard were blinded to the SOR values.

For Study 18, the average values of the left posterior putamen for the positive scans was 1.790 compared to the average values of the left posterior putamen for the negative scans of 2.627. The average SOR value calculated for negative PET scans is similar to that measured in normal subjects from the Applicant's previous retrospective study (2.545). The average SOR value for positive scans is reduced considerably relative to that of negative scans due to reduced uptake of ^{18}F-FDOPA which in turn is attributed to loss of dopaminergic neurons. The SOR values in the caudate and putamen of subjects with PS are expected to be lower than normal.

Observed overlap in the SOR values of Study #18 points to their limited diagnostic utility.

It should be noted that all patients on Study 18 received 150 mg carbidopa 60 minutes prior to ^{18}F-FDOPA Injection administration. The use of carbidopa may increase ^{18}F-FDOPA bioavailability to the brain by inhibiting peripheral decarboxylase activity and restricting peripheral ^{18}F-FDOPA metabolism.

The Applicant had not submitted any information on effect of other concomitant drug on the quality of ^{18}F-FDOPA injection. An information request was sent to the Applicant to "describe drug interaction potential for ^{18}F-FDOPA and effect of the concomitant drugs on ^{18}F-FDOPA PET images. Include discussion of the following drugs: 1) Haloperidol, 2) Monoamine oxidase inhibitors, 3) Reserpine, 4) Aripiprazole, and 4) Dopamine agonist and antagonist drugs." The Applicant submitted the concomitant medications taken by each patient. The data showed that for all patients with the standard of reference, 34 patients received no concomitant medication for movement disorder and were roughly equally distributed across positive and negative scans. 15 patients were taking levodopa in some form and this group had both positive and negative scans. Use of other medication combinations was limited to small numbers of subjects and could not be reliably interpreted.

The Applicant's data showed that in patients with a reference standard diagnosis of PS, no dopamine agonists, amantadine, anticholinergics, or catechol-O-methyltransferase (COMT) inhibitors were used. The Applicant has not conducted any concomitant drug effect study on the quality of ^{18}F-FDOPA PET scan. Patients with PS could potentially be taking dopamine agonists, dopamine re-uptake inhibitors, and other dopamine releasing agents such as psychostimulants of the amphetamine class that could affect the quality of ^{18}F-FDOPA scan as per literature reports. Therefore, the following labeling language is recommended for Section 7 of package insert:

> Aromatic L-amino acid decarboxylase (AADC) inhibitors
> Prior to Fluorodopa F 18 Injection administration, use of AADC inhibitors (e.g., carbidopa, benserazide, etc.) may increase Fluorodopa F 18 bioavailability to the brain by inhibiting peripheral decarboxylase activity and restricting peripheral Fluorodopa F 18 metabolism *[see Dosage and Administration (2.3)].*
>
> Dopamine agonists, dopamine reuptake inhibitors, dopamine releasing agents (DRAs), peripheral catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase (MAO) inhibitors
> Therapy for Parkinson's syndromes includes dopamine agonists, dopamine reuptake inhibitors, dopamine releasing agents (DRAs) such as psychostimulants of the amphetamine class, peripheral catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase (MAO) inhibitors. Whether discontinuation of these drugs prior to Fluorodopa F 18 administration may minimize the interference with a Fluorodopa F 18 image is not fully known; however, if use of these drugs can be safely suspended, discontinue use 12 hours before administration of Fluorodopa F 18 Injection *[see Dosage and Administration 2.3)]*.

7. Sources of Clinical Data and Review Strategy

In response to the 2016 FDA CR letter in which FDA identified serious design and conduct deficiencies in clinical Study #17, the Applicant conducted a new prospective clinical study (Study #18) under the Expanded Access IND 78861 for ^{18}F-FDOPA at the Feinstein Institutes. Since Study #18 was submitted to address the clinical and statistical deficiencies listed in the FDA CR Letter, the current review is focused on this study.

The current review also summarizes relevant clinical studies from prior review cycles that are supportive of ^{18}F-FDOPA efficacy for the proposed indication.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study #18

Overview and Objective

The protocol for Study #18 was submitted by the Applicant in response to the 9/15/16 CR letter issued by the FDA following the review of the re-submitted NDA 200655 containing Study #17. Study #18 was designed to address deficiencies cited in the CR letter and planned to recruit a minimum of 50 patients with possible PS. The primary objective of the study was to assess the imaging performance ^{18}F-FDOPA PET in 3 blinded readers relative to a clinical reference standard generated through at least 6 months of patient follow-up.

Trial Design

Study #18 was a prospective, single center study. Binary interpretations of ^{18}F-FDOPA scans by 3 independent readers were analyzed for agreement with a clinical reference standard of PS or non-PS, as established by a minimum of 6 months of patient follow-up.

Enrollment Criteria and Patient Population (Disease Characteristics)

Enrollment Criteria: All patients had to be 18 years of age or older with at least one of the cardinal symptoms of PS (defined by the Applicant as bradykinesia, rigidity, tremor, and postural instability). The patients were referred by neurologists for further evaluation due to uncertainty of clinical diagnosis. Because the Applicant expected difficulty enrolling patients with at least 2 cardinal symptoms of PS, both Study #17 and #18 had pre-specified entry criteria of only at least one cardinal symptom. However, most of the patients enrolled in Study #18 had at least 2 cardinal symptoms at enrollment, as shown in Table 2 below.

Disease duration included those newly diagnosed (months) to those having the disease for years as also listed in Table 2.

Table 2. Cardinal Symptom(s) and Disease Duration of Each Patient at Study Enrollment

Subject ID	Symptom 1	Symptom 2	Symptom 3	Symptom 4	Disease Duration
(b) (4)					

Subject ID	Symptom 1	Symptom 2	Symptom 3	Symptom 4	Disease Duration
(b) (4)					

Source: Applicant response to FDA Clinical Information Requests Dated 06-28-2019 and 07-10-2019

Among the 56 patients who completed the study, 38 (68%) were male, 18 (32%) were female. Mean age was 66 years. Thirty-three of the patients had symptoms for 2 years or less.

Patient Disposition

Out of the 69 recruited patients, 68 patients underwent ^{18}F-FDOPA and 56 completed at least 6-month follow-up clinical assessment to establish the reference standard. The clinical follow-up period ranged from 6 to 9 months post-imaging in these 56 patients, all of whom were included in the analysis of efficacy.

Study Drug Dosing

Approximately 5 mCi of ^{18}F-FDOPA (range from 4.5-5.5 mCi) was administered by intravenous injection. The F-DOPA mass dose ranged from (b) (4) mg per injection. Approximately one hour before dosing with ^{18}F-FDOPA, patients were administered 150 mg of carbidopa orally to block peripheral metabolism of ^{18}F-FDOPA. A 150 mg dose of carbidopa was selected from the investigator's own experience as well as that described in other peer-reviewed publications.

Image Acquisition and Interpretation

Approximately 70 minutes following ^{18}F-FDOPA administration, patients voided the bladder. PET images of the brain were collected for 20 minutes starting 80 minutes after ^{18}F-FDOPA administration.

Three readers blinded to patient clinical information independently interpreted ^{18}F-FDOPA PET images visually. The scan images had all identifiable marking removed.

The 3 readers evaluated the shape and size of the putamen and caudate bilaterally. Reduced PET signal in the putamen or both putamen and caudate, unilaterally or bilaterally, was interpreted as a positive scan. Normal comma-shaped activity in the putamen and caudate bilaterally was interpreted as a negative scan.

Standard of Reference

Clinical diagnosis at 6 to 9 months after ^{18}F-FDOPA PET was used as the reference standard. This reference standard clinical diagnosis was established by a single movement disorder specialist through clinical evaluation of each patient at baseline (prior to the PET scan) and at follow-up a minimum of 6 months after the PET scan. The movement disorder specialist was not a referring physician. At all times, the movement disorder specialist was blinded to ^{18}F-FDOPA PET results and any clinical information collected by referring physicians. Serial patient evaluation allowed the movement disorder specialist to assess interval change in signs and symptoms or interval response to trial therapy.

At baseline and at follow-up, the movement disorder specialist classified each patient as PS ("Dopaminergic Degeneration" per case report form) or non-PS ("No Dopaminergic Degeneration" per case report form). The categorization at follow-up was used as the reference standard in the study. Of note, the movement disorder specialist was not reminded of their own baseline diagnoses at the time of follow-up evaluation. Of the 56 patients who completed follow-up, 33 patients were categorized as PS and 23 patients were categorized as non-PS. In approximately 80% (45/56) of patients, the movement disorder specialist's categorization of PS

or non-PS was concordant at baseline and follow-up, indicating a high level of reproducibility of clinical evaluations.

To improve upon weaknesses in the reference standard of Study #17, Study #18 included detailed case report forms that were completed by the movement disorder specialist both at baseline clinical evaluation and follow-up clinical evaluation. One of these case report forms was the Unified Parkinson Disease Rating Scale (UPDRS), a standardized and well-accepted clinical tool for the evaluation of patients with Parkinsonian symptoms.

The UPDRS is divided into the following 4 sections:

1) Mentation, behavior, and mood
2) Activities of daily living
3) Motor examination
4) Complications of therapy

Each section of the UPDRS contains multiple questions or items that add to a final score of 0 to 199 points. Baseline and follow-up UPDRS scores of the 56 patients who completed the study were provided in the Applicant's submission.

In addition to the UPDRS, the movement disorder specialist completed a survey at each clinical evaluation for the presence or absence of 21 diagnostic features as well as a separate list to weigh evidence of a PS diagnosis against evidence of a non-PS diagnosis. Another case report form captured the final classification of PS or non-PS at each clinical evaluation. On this form, the movement disorder specialist also chose from a more detailed list of sub-diagnoses for exploratory purposes. At follow-up evaluation, the PS patient category included the following sub-diagnoses:

- Parkinson's disease
- Parkinson's disease with dementia
- Progressive supranuclear palsy
- Corticobasal degeneration
- Multiple systems atrophy
- Non-specific Parkinsonism

At the follow-up evaluation, the non-PS patient category included the following sub-diagnoses:

- Essential tremor
- Non-specific tremor
- Non-specific gait disorder
- No movement disorder
- Psychogenic Parkinsonism
- Vascular Parkinsonism
- Drug induced Parkinsonism
- Dystonia and dystonic tremor

Of note, ^{18}F-FDOPA PET was evaluated for its ability to distinguish between PS and non-PS groups, but not to identify a particular sub-diagnosis.

Data Quality/Integrity and Compliance With Good Clinical Practices

The Applicant did not submit a statement attesting that Study #18 was conducted in accordance with Good Clinical Practice. The study was conducted under an expanded access IND. The Applicant emphasized in the resubmission that the study was conducted under Institutional Review Board (IRB) oversight.

In previous review cycles, the FDA worked with the Applicant to develop case report forms to document data collection and avoid potential bias (e.g. by unblinding of PET readers). In addition to the movement disorder specialist's case report forms discussed above for establishing the clinical reference standard, there were 6 additional case report forms used to collect imaging data and other clinical information in Study #18.

- Case Report Form #1 collected the initial clinical diagnosis of the referring physician.
- Case Report Form #2 documented study eligibility.
- Case Report Form #3 recorded adverse events during the day of ^{18}F-FDOPA administration.
- Case Report Form #4 recorded adverse events at telephone safety follow-up.
- Case Report Form #5 recorded the Striatal Occipital Ratio (SOR) values for the left and right putamen and caudate. The SOR was calculated after the blinded PET reading for exploratory purposes.
- Case Report Form #6 recorded ^{18}F-FDOPA PET interpretations as positive or negative by a single PET reader.

Blank copies of each case report form were provided in the submission. A blank adverse event tracking log was also provided. Overall, the review team had no concerns regarding data quality and integrity.

Efficacy Results – Primary Analysis

The primary endpoints of Study #18 were positive percent agreement (PPA) and negative percent agreement (NPA) between binary ^{18}F-FDOPA PET results (positive or negative) and the binary reference standard clinical diagnosis at follow-up (PS or non-PS). PPA is defined as the percentage of patients with positive ^{18}F-FDOPA PET results among all patients with a clinical reference standard of PS. NPA is defined as the percentage of patients with negative ^{18}F-FDOPA PET results among all patients with a clinical reference standard of non-PS. While these definitions of PPA and NPA mathematically might equate to sensitivity and specificity, respectively, the review team believes that PPA and NPA are more appropriate terms for Study #18 since a clinical reference standard is not as definitive as a histopathological truth standard.

The following table shows PPA and NPA of each reader relative to the clinical reference standard.

Table 3. Performance of Three ^{18}F-FDOPA PET Readers

n=56 Patients	Positive Percent Agreement (95% CI) (% Patients With a Positive ^{18}F-FDOPA PET Among Patients With PS)	Negative Percent Agreement (95% CI) (% Patients With a Negative ^{18}F-FDOPA PET Among Patients With non-PS)
Reader 1	73 (55, 87)	91 (72, 99)
Reader 2	49 (31, 67)	91 (72, 99)
Reader 3	58 (39, 75)	83 (61, 94)

Source: Table 8 of this review

While all 3 readers demonstrated relatively high NPA values, the lower bound of the 95% CI for PPA extended below 50% in Reader 2 and Reader 3.

Efficacy Results – Exploratory Brain Regional Quantitative ^{18}F-FDOPA Uptake Analysis

The Applicant also conducted an exploratory quantitative analysis of ^{18}F-FDOPA PET based on uptake measurements in 6 striatal brain regions: left posterior putamen, right posterior putamen, left anterior putamen, right anterior putamen, left caudate, and right caudate. Each region's ^{18}F-FDOPA uptake was compared to the uptake in the occipital lobe, which was used as an internal control region to calculate the Striatal Occipital Ratio (SOR).

The following table lists the range of SOR values and the average SOR values for the 6 brain regions in all 56 patients completing the study, categorized by the binary ^{18}F-FDOPA PET interpretation of reader 1.

Table 4. Regional Striatal/Occipital Ratio (SOR) in Scan Positive and Negative Patients

Result	Left P Put	Right P Put	Left A Put	Right A Put	Left Caudate	Right Caudate
Scan positive range	1.446-2.268	1.392-2.472	1.647-3.210	1.636-2.899	1.930-3.262	1.938-3.324
Scan positive average	1.790	1.736	2.293	2.263	2.581	2.573
Scan negative range	1.899-3.486	1.717-3.288	1.964-4.125	2.067-4.107	2.034-4.117	1.966-4.087
Scan negative average	2.627	2.543	3.063	3.023	3.104	3.080

Source: Tables 11 and 12 of Study #18 Clinical Study Report

In all 6 striatal brain regions, the SOR ranges overlap in patients with ^{18}F-FDOPA PET interpreted visually as negative or positive. This overlap in range appears to limit the potential clinical utility of quantitative analysis of ^{18}F-FDOPA PET. No further exploration of the performance of SOR was undertaken.

8.1.2. Major Review Findings From Prior Review Cycles

Major Review Findings of NDA Submission Dated October 23, 2012

This prior 505(b)(2) NDA submission was predominantly literature-based. It contained the Applicant's own retrospective chart review of clinical experience at the Feinstein Institutes (Study #15), a publication (Study #16) of clinical follow-up of a subset of subjects in Study #15, and 7 additional publications. Overall, the FDA review found the submitted clinical data to be

inadequate to support the proposed indication and issued a CR letter dated 10/22/2013. The FDA recommended that the Applicant conduct a prospective clinical study to support the proposed indication.

The main study, Study #15, was based on a retrospective chart review of 185 patients and 11 normal controls at the Applicant's institution. Out of the 185 patients, 158 were positive on ^{18}F-FDOPA PET and responded to Parkinson's disease drug treatment (e.g. levodopa). The other 27 patients were negative on ^{18}F-FDOPA PET and did not respond to Parkinson's disease drug treatment. The Applicant inferred that positive ^{18}F-FDOPA PET results in the 158 patients correctly indicated loss of dopaminergic neurons in these patients. The Applicant further inferred that negative ^{18}F-FDOPA PET results in the 27 patients correctly indicated the absence of dopaminergic neurons loss in these patients. The review team concluded that the study had serious deficiencies including lack of a pre-specified protocol and use of an invalid standard of reference. Furthermore, the FDA inspection confirmed that the study did not meet Good Clinical Practice standards.

Of the additional 7 publications, most did not provide relevant clinical data to demonstrate the efficacy of ^{18}F-FDOPA in the product's intended population for the proposed indication. However, the review team considered one publication that compared ^{18}F-FDOPA PET to an approved comparator, I-123 FP-CIT SPECT (DaTscan), to be supportive of efficacy:

Eshuis et al.[7] Direct comparison of FP-CIT SPECT and F-DOPA PET in patients with Parkinson's disease and healthy controls

This study was conducted at a single center in Europe and evaluated 11 early-stage PD patients, 17 advanced-stage PD patients, and 20 age-matched healthy control subjects. Early-stage PD patients had disease duration of less than 3 years and were not using anti-Parkinson's medication. Advanced-stage PD patients had disease duration of 5 to 15 years and were using anti-Parkinson's medication with a documented response. All PD patients had at least 2 cardinal symptoms of PD.

Each of the PD patients in the study underwent I-123 FP-CIT SPECT and ^{18}F-FDOPA PET. Each control subject had either I-123 FP-CIT SPECT or ^{18}F-FDOPA PET (10 in each group). Semi-quantitative striatooccipital ratios (SOR) were obtained in 6 brain regions (bilateral putamen, bilateral caudate, and bilateral striatum). FP-CIT SPECT and FDOPA PET scans in PD patients were considered abnormal when the SOR values were less than 2 standard deviations below the mean SOR values of the healthy controls. Receiver operating curves (ROC) were produced and sensitivity and specificity were calculated.

The study reported similar semi-quantitative performance characteristics between ^{18}F-FDOPA PET and an approved imaging comparator for differentiation of patients with PD from heathy subjects. The study is considered supportive.

[7] Eshuis et al. Direct comparison of FP-CIT SPECT and F-DOPA PET in patients with Parkinson's disease and healthy controls. Eur J Nucl Med Mol Imaging (2009) 36:454–462

Major Review Findings of NDA Resubmission Dated December 15, 2015

The submission included a prospective clinical study (Study #17) with a design similar to that of Study #18. A total of 45 patients completed Study #17 under an expanded access IND at the Applicant's own institution. FDA review found this study to have several critical deficiencies related to the clinical standard of reference as follows from the CR letter dated 09/15/2016:

1. A substantial number of patients did not complete clinical follow-up at the pre-specified minimum time interval of 1-year:
    - Out of the 32 patients with positive ^{18}F-FDOPA PET results, only 20 patients had clinical follow-up at the pre-specified interval of at least 1-year to serve as a reference standard.
    - Out of the 13 patients with negative ^{18}F-FDOPA PET results, only 5 patients had any clinical follow-up to serve as a reference standard and only one of these patients had clinical follow-up at the pre-specified interval of at least 1-year.
2. Potential bias in generation of the reference standard related to the fact that ^{18}F-FDOPA PET results were known to the reference standard clinicians prior to their determination of follow-up patient diagnosis.

During this review cycle the FDA review team consulted two independent Special Government Employee (SGE) consultants who were both members of FDA MIDAC (Medical Imaging Drug Advisory Committee). See Section 9 for further information regarding this consultation.

8.1.3. Additional Literature Support

In addition to the Eshuis et al. (2009) study described above, the FDA identified the following publication from a literature search it conducted during the last review cycle ending in 2016.

N. Ibrahim et al: The sensitivity and specificity of F-18 FDOPA PET in a movement disorder clinic, American Journal of Medical Molecular Imaging 2016; 6 (1): 102-109

This retrospective study analyzed 27 patients who underwent ^{18}F-FDOPA PET for motor symptoms suspicious for PD between 2001 to 2008 at the University of Wisconsin. The patients' medical records were assessed for clinical course of illness, response to levodopa, and length of follow-up. The eventual diagnosis by a referring neurologist after at least 2 years of clinical follow-up (range 2-9 years) was used as the reference standard.

Patients were premedicated with 200 mg of carbidopa orally 1 hour prior to the injection of 5 to 10 mCi of ^{18}F-FDOPA. Three nuclear medicine physicians interpreted the ^{18}F-FDOPA PET scans in a binary fashion similar to the method used in Study #18. The publication reported that out of a total of 28 ^{18}F-FDOPA PET scans, one was false negative, 20 were true positives, and 7 were true negatives. No false positive results were reported.

A strength of the study was that patients were followed clinically for at least two years to establish the standard of reference. However, several weaknesses of the study limit its support for imaging efficacy. Similar to Study #17, the physician who made the reference standard clinical diagnosis was not blinded to ^{18}F-FDOPA PET results. In addition, the PET readers were

aware of initial clinical data and other imaging results that were available at the time of the PET acquisition.

8.1.4. Integrated Assessment of Effectiveness

Study #18 had a well-controlled, prospective design and adequately addressed the deficiencies cited in the previous FDA CR letter from 2016. The study evaluated 56 adult patients with at least one cardinal Parkinsonian symptom for whom a referring clinician had diagnostic uncertainty. The majority of these patients had symptoms for 2 years or less and therefore represented the anticipated population of predominant intended clinical use. A minimum of 6 months of clinical follow-up by a movement disorder specialist was used as the reference standard to categorize patients as PS or non-PS. Such a clinical reference standard is commonly employed in studies of PS due to the infeasibility of obtaining histopathological confirmation of disease. The movement disorder specialist in Study #18 used standardized clinical assessments for PS and was blinded to ^{18}F-FDOPA PET images and interpretation results. Three blinded readers independently interpreted ^{18}F-FDOPA PET images as either positive or negative. While the study found a relatively low positive percent agreement (with a point estimate range of 49% to 73% for 3 readers) between ^{18}F-FDOPA PET reads and the reference standard of clinical follow-up, high negative percent agreement was demonstrated by all 3 readers (with a point estimate range of 83% to 91%).

8.2. Review of Safety

8.2.1. Review of the Safety Database

Study #18 added 68 patients to the prior experience in 53 patients who were administered ^{18}F-FDOPA in Study #17. Patients from Study #17 are included in the safety database because deficiencies only impacted efficacy assessment rather than safety assessment in that study. In total, Study #17 and Study #18 provided a combined experience in 121 patients who had safety assessment procedures prespecified in study protocols and safety data recorded on detailed case report forms.

In prior review cycles, the Applicant submitted a retrospective chart review from their own institution (Study #15). In Study #15, an additional 196 subjects were injected with ^{18}F-FDOPA, including 185 patients and 11 normal control subjects. The Applicant reported no adverse reactions in Study #15. However, since there was no prespecified safety assessment protocol, this limited safety information from Study #15 is only considered as supportive.

In addition to the safety data from the Applicant's studies, potential safety issues from published literature were assessed.

8.2.2. Safety Results

In Study #17 and #18, all patients were observed for any physical discomfort during ^{18}F-FDOPA PET visits and adverse events were collected. After the PET scans, patients were contacted by phone within 24 hours to collect information regarding any additional adverse events.

Safety Results From Study #18

Table 5 below summarizes safety results from Study #18. There were no deaths or serious adverse events observed. All 12 observed adverse events (AEs) were mild in severity and resolved without intervention. The principal investigator assessed all AEs as unlikely to be related ^{18}F-FDOPA.

Table 5. Summary of Adverse Events Collected From Patients in Study #18

Adverse Event	No. of Subjects	Severity	Relationship	Serious	Resolved	Comment
Headache	n=2	Mild	Unlikely	No	Yes	
Barking	n=1	Mild	Unlikely	No	Yes	Patient was on antipsychotic Medication
Lightheadedness	n=1	Mild	Unlikely	No	Yes	
Right side pain near liver	n=1	Mild	Unlikely	No	Yes	
Tiredness	n=3	Mild	Unlikely	No	Yes	
Leg pain	n=1	Mild	Unlikely	No	Yes	
Nausea	n=1	Mild	Unlikely	No	Yes	
Urine Retention	n=1	Mild	Unlikely	No	Yes	History of Prostate issues
Diarrhea	n=1	Mild	Unlikely	No	Yes	

Source: Table 14 of Study #18 Clinical Study Report

Safety Results From Study #17

There were no deaths or serious adverse events observed in Study #17. All AEs were mild in severity and resolved without intervention.

One patient in Study #17 reported a bruise and slight swelling 2 days after the scan, possibly at the ^{18}F-FDOPA injection site following intravenous catheter placement. There was no infection at the site and the AE resolved. The study investigators considered this AE to be possibly related to the study drug. All other AEs observed in Study #17 were considered unlikely to be related to ^{18}F-FDOPA by the Applicant.

8.2.3. Safety Issues From Published Literature

In a publication by Koopmans et al. (2005),[8] one case of the induction of carcinoid crisis after rapid intravenous injection of ^{18}F-FDOPA was reported in a patient referred for imaging of metastatic carcinoid. However, no induction of carcinoid crisis was observed by Nataf et al.

[8] Koopmans, K., Brouwers, A., De Hooge M., Van der Horst-Schrivers, A., Kema, I., Wolffenbuttel, B., De Vries, E., Jager, P. (2005), Carcinoid crisis after injection of 6-18F-fluorodihydroxyphenylalanine in a patient with metastatic carcinoid. J. Nucl. Med., 46,
1240-1243.

(2006)[9] in a similar population of 170 patients (majority referred for carcinoid tumors) exposed to ^{18}F-FDOPA over a period 4 years. While both studies administered a similar volume (roughly 8 mL), Nataf el al. injected the dose slowly over 1 min compared to the several second injection of Koopmans et al.. Another important difference between the two groups was the specific activity of ^{18}F-FDOPA preparations. In the case reported by Koopmans et al., specific activity was 6 GBq/mmol, whereas Nataf et al. used a commercial preparation with a 5-fold greater specific activity of at least 30 GBq/mmol at calibration.

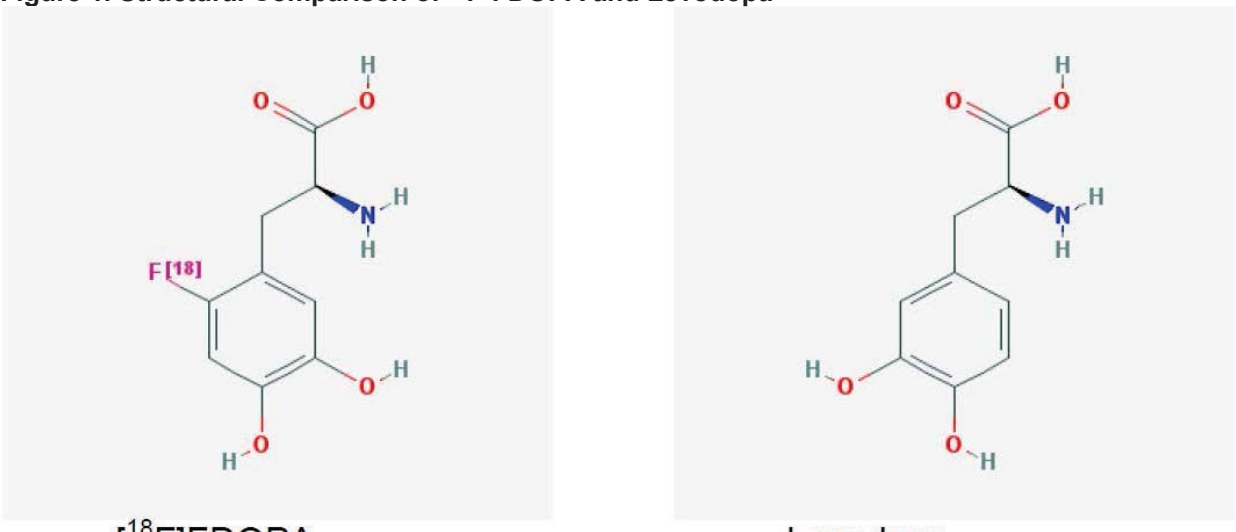
In an appended reply to Nataf et al., Koopmans et al. performed described another 100 ^{18}F-FDOPA PET scans performed with slow injection over 3 min without any witnessed reactions. Koopmans et al. concluded that rapid injection together with relatively low specific activity of ^{18}F-FDOPA could potentially result in a first-pass bolus effect that might have had enough pharmacologic activity to trigger carcinoid crisis in their original patient with known metastases.

Of note, in the Nataf et al. study, the rate of intravenous injection of ^{18}F-FDOPA was slowed to diminish a transient and mild burning sensation at the injection site that had been reported in clinical experience. The mechanism of this adverse event was thought to be related to the acidic pH of the administered ^{18}F-FDOPA preparation (pH 4.5–5).

8.2.4. Integrated Assessment of Safety

^{18}F-FDOPA is structurally similar to the therapeutic drug, levodopa, with the only difference being the presence of an F-18 atom instead of a hydrogen atom at position 6 of the aromatic ring, as shown in the following figure.

Figure 1. Structural Comparison of ^{18}F-FDOPA and Levodopa



Source: Left: https://pubchem.ncbi.nlm.nih.gov/compound/56494#section=2D-Structure;
Right: https://pubchem.ncbi.nlm.nih.gov/image/fl.html?cid=6047]

[9] Nataf, V., Balard, M., De Beco, V., Kerrou, K., Gutman, F., Grahek, D., Montravers, F., Talbot, J. (2006), Safety of 18F-DOPA injection for PET of carcinoid tumor. J. Nucl. Med., 47, 1732.]

Oral levodopa has been used for treatment of Parkinson's disease for over 40 years at doses ranging up to 2000 mg/day. For comparison, the one-time intravenous mass dose of ^{18}F-FDOPA in Study #18 ranged from (b) (4) mg. Given the high bioavailability of oral levodopa, ^{18}F-FDOPA safety is supported by the extensive clinical experience with much higher and repeated dosing of the this closely related drug. Similarly, the basic adverse event collection performed in the Applicant's clinical studies is sufficient without additional detailed safety monitoring such as laboratory testing.

Adverse event information from the 121 patients exposed to ^{18}F-FDOPA in Study #17 and Study #18 raises no safety concerns. All reported AEs were mild in severity, non-serious and resolved without intervention. Only one case of bruising and swelling near the injection site was assessed as possibly related to ^{18}F-FDOPA by an investigator, but more likely was related to intravenous catheter placement. Additionally, no adverse reactions were reported in 196 patients who were administered ^{18}F-FDOPA in Study #15, although formal adverse event monitoring was not prespecified.

A single published report of carcinoid crisis appears possibly related to ^{18}F-FDOPA injection. Other published data suggest mitigation of this potential risk by slowing the rate of ^{18}F-FDOPA injection. In any event, a slower rate of ^{18}F-FDOPA injection seems reasonable given its acidic pH and published clinical experience with presumably related transient mild burning sensation at the injection site of some patients. Of note, foreign labeling for ^{18}F-FDOPA recommends slow intravenous injection over approximately one minute (Chevalme et al. (2007)).[10]

8.3. Statistical Issues

For regulatory statistical history, the reader is directed to the following table.

[10] Chevalme, Yanna-Marina, Montravers, Françoise, Vuillez, Jean-Philippe, Zanca, Michel, Fallais, Charles, Oustrin, Jean, & Talbot, Jean-Noël. (2007). FDOPA-(18F): a PET radiopharmaceutical recently registered for diagnostic use in countries of the European Union. *Brazilian Archives of Biology and Technology*, *50*(spe), 77-90.

Table 6 U.S. FDA Regulatory Actions

Date	Purpose	Conclusion
October 30, 2009	Submitted NDA based on peer-reviewed publications.	FDA refused to file the application because the submission did not contain adequate information about dosing, risk-benefit analysis, to allow a substantial review.
October 22, 2012	Submitted NDA based on a retrospective chart review of 185 patients at the Applicant's institution.	The FDA review team found the submitted clinical data to be inadequate to support the proposed indication and issued a Complete Response (CR) letter dated 10/22/2013. The FDA recommended the Applicant conduct a prospective clinical study to support the proposed indication.
December 15, 2015 Applicant's Study #17	The resubmission included a prospective clinical study of 45 patients that was conducted under the expanded access IND at the Applicant's own institution.	FDA review team found this study to be poorly conducted with a substantial percentage of patients lacking the prespecified one-year clinical follow-up as the standard of reference. In addition, FDA review team noted that the PET image interpretation was known to the clinicians conducting the follow-up prior to their determination of the reference standard clinical diagnosis, leading to potential bias in the standard of reference. FDA again issued a Complete Response (CR) letter dated 09-15-2016.
April 10, 2019 Applicant's Study #18	This resubmission is based on a new prospective clinical study under expanded access IND at the Applicant's own institution of 56 enrolled patients who completed the study procedures.	The deficiencies cited in Study #17 have been addressed in the Applicant's resubmission of Study #18. The study #18 protocol was reviewed and agreed upon by the FDA review team.

This section focuses on the data generated in Study #18. Using that data, the statistical review team produced the following table.

Table 7. Performance of ^{18}F-FDOPA PET Readers Relative to Reference Standard in Study #18

	Reader 1			Reader 2			Reader 3		
Final SOR*	+	-	Total	+	-	Total	+	-	Total
PS	24	9	33	16	17	33	19	14	33
non-PS	2	21	23	2	21	23	4	19	23
Total	26	30	56	18	38	56	23	33	56
Positive percent agreement (%)	73			49			58		
95% CI** (%)	(55, 87)			(31, 67)			(39, 75)		
Negative percent agreement (%)	91			91			83		
95% CI** (%)	(72, 99)			(72, 99)			(61, 94)		

*: SOR: Standard of Reference
**: 95% CI are based on Exact Binomial Test

^{18}F-FDOPA PET imaging has high negative percent agreement with the clinical reference standard (i.e., ^{18}F-FDOPA PET is highly specific). This result was observed in all other previous studies.

^{18}F-FDOPA PET imaging has low positive percent agreement with the clinical reference standard, as demonstrated by the lower bound of the 95% CI being less than 50% for 2 out of the 3 readers. Hence ^{18}F-FDOPA injection should only be used as an adjunct to other diagnostic evaluations.

Efficacy Results in Subgroup Populations Based on Duration of Disease

Disease duration included those newly diagnosed (months) to those having the disease for years. The clinical review team identified duration of disease of 2 years or less as defining an important and clinically relevant subgroup of patients with early disease. The following table gives the results of ^{18}F-FDOPA PET readers' performance for this subgroup of 33 patients.

Table 8. Performance of ^{18}F-FDOPA PET Readers for Subgroup With Disease Duration ≤2 Years

	Reader 1			Reader 2			Reader 3		
Final SOR*	**Positive**	**Negative**	**Total**	**Positive**	**Negative**	**Total**	**Positive**	**Negative**	**Total**
PS	16	5	21	9	12	21	12	9	21
non-PS	1	11	12	0	12	12	2	10	12
Total	17	16	33	9	24	33	14	19	33
PPA (%)	76			43			57		
95% CI**	(53, 72)			(22, 66)			(34, 78)		
NPA (%)	92			100			83		
95% CI**	(62, 100)			(74, 100)			(52, 98)		

*: SOR: Standard of Reference
**: 95% CI are based on Exact Binomial Test

These analyses show that the results between this subgroup and the overall population are consistent. Other subgroups are based on gender and age of the patients. The statistical review team also analyzed these subgroups and found consistency with overall population results. This consistency demonstrates that the benefits and limitations of ^{18}F-FDOPA PET imaging apply to various subgroups as well.

8.4. Conclusions and Recommendations

Study #18 adequately addressed the deficiencies identified in the Applicant's previous NDA submissions. While the study found a relatively low positive percent agreement between ^{18}F-FDOPA PET reads and the reference standard of clinical follow-up, high negative percent agreement was independently demonstrated by all 3 readers. Subgroup analysis revealed similar performance of ^{18}F-FDOPA in a clinically relevant population of patients who had symptoms for 2 years or less. ^{18}F-FDOPA safety is supported by extensive clinical experience with much higher and long-term dosing of the closely related therapeutic drug, levodopa. Available safety data from clinical trials demonstrate a benign safety profile for ^{18}F-FDOPA. The review team recommends approval of ^{18}F-FDOPA PET imaging as an adjunct to other diagnostic evaluations in patients with suspected PS.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee meeting was conducted.

During the review cycle of the resubmitted NDA in 2016, the FDA review team consulted two independent Special Government Employees (SGE) for a review ^{18}F-FDOPA PET images from Study #17. Both consultants were well known nuclear medicine physicians and members of MIDAC (Medical Imaging Drug Advisory Committee). Neither consultant was aware of the other's participation. No clinical data were available to either consultant. Questions that were asked of the reviewer consultants appear below with a summary of their responses:

1. *Please comment on the likelihood of an ability in practice to discriminate between "positive" and "negative" patients based on these images. Please mark each image as adequate or inadequate for interpretation.*

Reviewer 1 found all images to be adequate with color images being less optimal than the black and white images. It was easy to tell apart negative from positive.

Reviewer 2 found all images easy to read in black and white and had not assessed color images at all. He characterized them all as adequate.

2. *Please comment on the spectrum of difficulty in interpreting the provided images and provide a binary assessment of diagnostic confidence in interpreting each image.*

Reviewer 1 felt that the spectrum of difficulty was reasonable and was confident in assessing every image.

Reviewer 2 rated diagnostic confidence on a scale from A to D, with A representing the highest level of confidence. The majority (34) of studies were ranked as A, 6 as B, and 5 as C.

3. *Do you agree with the submitted interpretation of the provided images?*

Reviewer 1 disagreed with interpretation of images in 4 out of 45 patients (2 positive and 2 negative).

Reviewer 2 disagreed in 5 out of 45 cases, all of which he considered to be positive whereas the on-site blinded readers interpreted them as negative.

10. Pediatrics

The Applicant stated that ^{18}F-FDOPA is not intended for pediatric patients. The proposed indication for ^{18}F-FDOPA is generally not applicable to pediatric patients because of the lack of PS pathophysiology in this population. Relevant pediatric studies with ^{18}F-FDOPA for the proposed indication would thus be impossible or highly impractical. On June 5, 2013, the FDA Pediatric Review Committee (PeRC) discussed the application and agreed with granting a full waiver of pediatric studies.

11. Labeling Recommendations

Section 1: Indications and Usage

- ^{18}F-FDOPA should be indicated for use in PET to visualize dopaminergic nerve terminals in the striatum for the evaluation of adult patients with suspected PS.
- To reflect ^{18}F-FDOPA performance characteristics and the current field of PS diagnosis in general, ^{18}F-FDOPA PET should be described as an adjunct to other diagnostic evaluations.

Section 2: Dosage and Administration

- Radioactivity dose should be the same as that used in Study #18 (5 mCi).
- As in Study #18, peripheral dopaminergic blockade with 150 mg of oral carbidopa is recommended 60 to 120 minutes prior to the administration of ^{18}F-FDOPA. Of note, a maximum daily oral dose of 200 mg of carbidopa is FDA approved for co-administration with therapeutic levodopa.
- ^{18}F-FDOPA should be administered as an intravenous infusion over 1 minute to reduce potential injection site pain as reported in published foreign experience.
- A visual and binary image interpretation method is recommended using standard transaxial PET images of the brain.

Section 6: Adverse Reactions

- Clinical trials experience should describe the lack of adverse reactions in the 121 patients exposed to ^{18}F-FDOPA in Study #17 and Study #18.
- Injection site pain should be added to postmarketing experience to reflect published foreign findings.

Section 7: Drug Interactions

- This section of labeling should include the clinical pharmacology recommendations listed at the end of Section 6.1.1 of this review.

Section 14: Clinical Studies

- This section should describe Study #18 and include the PPA and NPA for each of the 3 readers along with the respective 95% CI.
- To reflect the performance characteristics of ^{18}F-FDOPA PET, Section 14 should state that effectiveness as a screening or confirmatory test has not been established.
- To reflect the design of Study #18, Section 14 should state that effectiveness of ^{18}F-FDOPA PET for monitoring disease progression or response to therapy has not been established.

12. Risk Evaluation and Mitigation Strategies (REMS)

None.

13. Postmarketing Requirements and Commitment

None.

14. CMC Executive Summary (Office of Pharmaceutical Quality OPQ)

OPQ recommends approval of NDA 200655 for ^{18}F-FDOPA, based on the OPQ N200655 Integrated Quality Assessment Final of 4/19/2016 and fulfillment of a commitment (PMC) to implement a GMP supply of precursor along with provision of supporting information on its GMP synthesis. With these fulfillments in place, the Applicant has provided adequate information to ensure the identity, strength, quality and purity of the proposed drug product.

15. Office Director Comments

I concur with the conclusion of the review staff that the application should be approved. The standard of truth is less than optimal and I agree that this test serves as an adjunct to other testing and clinical findings. The information in table 8 should be included in the clinical studies section of the label to allow a clinician to calculate the positive predictive value and negative predictive value.

16. Financial Disclosure

The Applicant states that they are only the manufacturer of this drug and have no connection or contact with any of the medical practitioners prescribing this imaging agent, and there are no financial interests between these medical practitioners and the Applicant (Feinstein Institutes for Medical Research).

The Applicant conducted three clinical studies onsite (Study #15, 17, #18). In previous submissions, the investigators, Dr. David Eidelbert, M.D. (Head for Neurosciences at Feinstein Institutes for Medical Research) and Dr. Thomas Chaly, Ph.D. (Chief of Cyclotron/Radiochemistry at the Feinstein Institutes for Medical Research) both signed and submitted FDA form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and reported no financial interests and arrangements.

For Study #18, the Applicant submitted a separate Form 3454 listing four investigators who conducted the study. None of the investigators had financial arrangements with the Applicant. None received payments from the Applicant.

Covered Clinical Study (Name and/or Number): Feinstein Institutes Study #18

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 4		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/s/

CHARLES J GANLEY
10/08/2019 01:38:55 PM

DMIP MEMORANDUM TO FILE
Medical Officer / ADL: Michele Fedowitz
NDA 200655 FDOPA
SDN 40, 41, 48

The sponsor submitted labeling for the current application in SDN 40 (1/21/2016) and 41 (1/29/2016). On March 23, 2016, the sponsor was sent and FDA Labeling information request to reflect correct dosimetry data expressed in proper accepted unit format:

"Table 1, pertaining to estimated values of radiation absorbed dose per administered activity from Fluorodopa F 18 Injection, is based on data that you cite from references 1-3, dating from 1985-1996. Since then there have been a number of advances in modeling and computation, as summarized in ICRP Publication 106, *Radiation Dose to Patients from Radiopharmaceuticals – A third amendment to ICRP Publication 53*, in the *Annals of the ICRP* Vol. 38, Issues 1-2, published by Elsevier for the International Commission on Radiological Protection, February-April 2008. The modeling and computational advances summarized in ICRP Publication 106 have been incorporated into updated estimates of radiation absorbed dose per administered activity of [^{18}F]Fluoro-L-DOPA, as tabulated in ICRP Publication 106 Table C.10.4 (p. 91). For example, for the bladder wall of an adult, the ICRP Publication 106 Table C.10.4 value is 0.30 mGy/MBq, (b) (4) .

Please update the estimates of radiation absorbed dose per administered activity according to ICRP Publication 106 or, if available, a more recent and authoritative source. Also, along with these updated values, please include updated units of measurement of radiation absorbed dose per administered activity in terms of "mGy/MBq" (cf. ICRU Report No. 85, *Fundamental Quantities and Units for Ionizing Radiation (Revised)*, published by The International Commission on Radiation Units and Measurements, October 2011.)"

The Sponsor responded the same day (March 23, 2016) with SDN 48 (labeling/Package Insert Draft) which included an update to Table 1. The updated tabulated values and SI units of the revised table were responsive to our IR, (b) (4)

Comments: The application was given an eventual complete response. Should the Sponsor respond, the issue of (b) (4) *to Table 1 will need to be addressed at future labeling meetings.*

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/s/

MICHELE B FEDOWITZ
10/04/2016

Office Director Decisional Memo

Date	September 15, 2016
From	Charles J. Ganley, M.D.
Subject	Office Director Decisional Memo
NDA **Supplement #**	NDA #200655 Number 50
Applicant Name	Feinstein Institute for Medical Research
Date of Submission	December 15, 2015
PDUFA Goal Date	September 15, 2015 (extended from June 15, 2015)
Proprietary Name / **Established (USAN) Name**	No Proprietary Name Fluorodopa F 18 (FDOPA F 18)
Dosage Forms / Strength	Injection / (b) (4) mCi/mL
Applicant Proposed Indication(s)/Populations	Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.
Action:	Complete Response

The Division Director memo has a complete list of review staff.

Summary Recommendation

The sponsor received a complete response (CR) letter on October 22, 2013 for chemistry deficiencies and clinical data deficiencies. Sufficient information has been submitted to address the chemistry deficiencies but the clinical trial that was conducted to respond to the clinical deficiencies was not adequately conducted. The study was missing important clinical patient follow-up data necessary for the determination of the standard of reference[1]. Additionally, the clinicians making the clinical diagnosis post-scan, which would serve as the standard of reference, were aware of the interpretations of the scans prior to the diagnosis. For these reasons, the study does not adequately address the clinical deficiency cited in the CR letter and does not support the approval of the drug for marketing. This memo concurs with the recommendations of the division director, CDTL and the statistical and clinical reviews to not approve the application. The sponsor needs to conduct additional studies or supplement the trial submitted if it can be salvaged. There are, however, serious problems with the conduct of the submitted study and the collection of data that raise serious concerns about the strength of this data and it use going forward.

Background Information

The CDTL memo provides a summary of the history of NDA 200655 and it will not be repeated in this memo. FDOPA F 18 is a radiopharmaceutical PET imaging agent being evaluated to aid in the diagnosis of parkinsonian syndromes relative to other diseases that may cause overlapping symptoms (e.g. essential tremor). Amino acid decarboxylase converts FDOPA to fluorodopamine (FDOPAMINE) in the brain.[2] FDOPAMINE is taken up by dopaminergic neurons. FDOPAMINE accumulates in the dopaminergic neurons in basal ganglia of the brain. In diseases with a depletion of the number of dopaminergic neurons, such as Parkinson's Disease, FDOPA F 18 PET could serve as a possible tool to differentiate Parkinsonian Syndromes (PS) pathology[3] from

[1] To establish efficacy in clinical studies, we recommend that the functional, physiological, or biochemical measurements of the medical imaging agent be compared with those of a reference product or a procedure of known high validity (i.e., a truth standard). Ideally, we recommend that the high validity of this reference product or truth standard be documented thoroughly and critically before its use in clinical studies intended to demonstrate effectiveness of the test imaging agent. There is no truth standard in this study. In lieu of the stand of truth, the clinical diagnosis after 1 year of follow-up served as a standard of reference to assess the performance of the FDOPA F 18 scans.

[2] FDOPA is also metabolized by peripheral catechol-o-methyl transferase (COMT) before crossing the blood brain barrier. This can reduce uptake. Carbi-dopa is pre-administered to reduce COMT activity.

Non-Parkinsonian Syndromes (NPS)[4] pathology when there are difficulties in making a diagnosis for patients presenting with signs such as tremor.

The sponsor submitted a study report (study #17)[5] on 45 subjects who underwent FDOPA F 18 scanning. The prospective evaluation required each patient to be followed for 1 – 2 years and a clinical diagnosis, either PS or NPS, made based on clinical evaluation. The clinical diagnosis was to serve as the standard of reference (not the standard of truth). "Positive" scans are abnormal, indicative of decreased dopamine uptake in the striatum, and are suggestive of PS. "Negative" scans are normal scans, indicative of normal dopamine uptake, and are suggestive of NPS.

Results

Forty-five subjects were enrolled in an expanded access protocol and received FDOPA F 18. The scans were read by 3 readers, a physicist and 2 neurologists, and were determined to be positive or negative. In 44 of the 45 scans, there was 100 percent concurrence between the three readers. The results of the scans are as follows:

Scan Interpretation	Clinical Diagnosis (Standard of Reference)	Actual Follow-up	
		1 year or greater (patient #s)	Less than one year (patient #s)
32 Positive	2 lost to follow-up	0	2 (b) (6)
	30 PS	(b) (6)	(b) (6)
13 Negative	7 Lost to Follow-up	0 (b) (6)	(b) (6)
	6 NPS	1 (b) (6)	5 (b) (6)
Total		21	24

Sensitivity and specificity cannot be adequately calculated because a significant proportion of the patients are either lost to follow-up or had a follow-up of less than one year. Additionally, the clinicians making the clinical diagnosis were aware of the scan results at the time of follow-up. Nine subjects had no follow-up for the assessment of a clinical diagnosis. An additional fourteen subjects did not have follow-up for 1 to 2 years as specified per protocol. Because the clinicians were aware of the scan results, it is not clear whether that knowledge biased the final clinical diagnosis in follow-up by the clinician.

In table 2 of the April 26, 2016 statistical review, the diagnosis at referral is listed for 36 of the 45 patients. The following observations are relevant in the demonstration of the potential clinical utility.

- The 9 patients who did not have a clinical diagnosis at referral were also the 9 patients who were lost to follow-up after scan (no follow-up for clinical diagnosis). Seven of the nine had negative scans.
- Five patients[6] were diagnosed with NPS. At referral, three of them were thought to have PS and for two of them either PS or NPS were possible.

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[3] Parkinsonian Syndromes includes diseases manifested by a depletion of dopaminergic neurons in the basal ganglia. These conditions include but are not limited to Idiopathic Parkinson's Disease, Progressive Supranuclear Palsy, and Corticobasal Degeneration,

[4] Non-Parkinson Syndromes include diseases such as Essential Tremor, SWEDD (Scans Without Evidence of Dopaminergic Deficit) and Dopa-Responsive Dystonia.

[5] The study was conducted under an expanded access IND and the investigator was permitted to charge for the scan.

[6] Patient # (b) (6)

- Five other patients[7] had possible diagnoses of PS or NPS at referral. All five were diagnosed with PS.

The division had the scans reviewed by two special government employees (SGEs) with experience in reading FDOPA F 18 scans with the intent of determining the quality of the scans, whether the scans are readable and also to get input on their interpretation of the scans. Both SGEs felt the scan quality was good and they were all readable. For their reads, they agreed with each other on 40 of the 45 scan interpretations (89%). For the three readers in the study, they agreed with each other on 44 of the 45 scan interpretations (98%). It was noted in the statistical review that it is not clear from the report that the readers were blinded to clinical information and whether they worked independently of each other. There were six scans where at least one of the SGEs interpretations differed from the interpretation of the three readers. One of the patients had no follow-up and no diagnosis. For the remaining five scans, three were diagnosed with PS and two with NPS.

Conclusion

The study was poorly conducted. FDOPA F 18 image interpretation results were conveyed to the referring physician prior to the clinical diagnosis. As such, the clinical diagnosis may be influenced by the scan result which makes it difficult to depend on the clinical diagnosis as the standard of reference. Without confidence in the standard of reference, it is difficult to evaluate the performance of this test. There was no image interpretation charter or standardized reader training. It is not clear whether clinical information was provided to the readers for interpretation of the scan and whether they were read independently, both of which may bias their interpretations.

The clinical follow-up was poor. It is hard to understand why a referral diagnosis was not available in nine patients when this information should be easily obtainable. It is more understandable why follow-up post-scan was a problem because patients need to show up for their visits. The sponsor noted that they made attempts at follow-up but were unsuccessful. It is surprising, however, that more than half of the patients failed to have follow-up as per protocol especially for patients who were paying for the test out of pocket and had a vested interest in knowing the accuracy of the test.

I agree with the assessment of the division that this clinical data is not adequate. The first step is to determine whether this data can be salvaged. It may require a re-read of the scans but with a charter for image interpretation or some standardized reader training. Readers should be independent and not have prior knowledge of clinical history. For the determination of clinical diagnosis, it may not be sufficient to depend on the clinical diagnosis in this submission. An option would include having an independent clinician perform an examination of the patients and arrive at a clinical diagnosis. To do this, limited information could be provided to the clinician and the patient would have to be counseled not to reveal their diagnosis or previous test results. It would be difficult to have a clinical diagnosis derived from a chart review unless the information related to the results of the scan can be purged and if the information is limited to clinical symptoms and clinical course. Attempts can be made to contact the patients lost to follow-up.

The division recommends that new patients be continued to be enrolled to supplement this study. That would be acceptable but only if there are substantial changes in how the study is conducted, particularly as to how the reads are conducted and the withholding of scan results from the person making the clinical diagnosis. Follow-up of patients needs to be improved. This data was obtained under an expanded access protocol. The division should determine whether the current protocol includes sufficient measures to encourage collection of information to support a marketing application or whether changes to the protocol need to be made.

The chemistry deficiencies in the CR letter were adequately addressed. A PMC was agreed upon for this cycle in the event that the application was approved. The sponsor submitted the information that was to be included in the PMC just prior to the current PDUFA data. This information was not reviewed and will be addressed in the next cycle.

[7] Patient # (b) (4)

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/s/

CHARLES J GANLEY
09/15/2016

Medical Officer Review
Amendment to Review of NDA 200655

Date:	**September 2, 2016**
From	**Brenda Ye, MD**
NDA # and Supplement #	**NDA 200655, Supporting Document #50**
Applicant	**Feinstein Institute for Medical Research**
Date of Original Submission	**December 15, 2015**
Original PDUFA Goal Date	**June 15, 2016**
Date of Major Amendment	**April 11, 2016**
Proprietary Name / Established	**Florodopa-F-18 Injection**
Dosage forms / Strength	**Solution for Injection, 0.42-8.33 mCi/mL**
Proposed Indication(s)	**Positron Emission Tomography (PET) imaging visualization of dopaminergic** (b) (4) **in striatum of adult patients with suspected parkinsonian syndromes (PS)**
Recommended:	**Complete Response**

The Major Amendment

In response to FDA request, the applicant submitted FDOPA PET images for all 45 patients in the clinical study conducted by the Feinstein Institute of Medical Research (Study #17). All patient information was de-identified in the submission. The FDOPA PET image submission, dated 04/08/16 (received 04/11/16), was determined by the FDA review team to be a major amendment. Along with the FDOPA PET images, image interpretation (positive/negative) for each patient was also submitted.

The reason for the FDA's request and designation as a major amendment is that the application is supported by a very limited clinical database (n = 45) and the clinical team would like to assess whether the images obtained and interpreted by the applicant represent the spectrum of images which would be typically obtained and interpreted if FDOPA were to be used in clinical practice.

Review of FDOPA PET images by the clinical team

The clinical team has independently reviewed the submitted FDOPA PET images. Each patient's image set includes axial PET images through the brain and a composite image integrating underlying positron emission data through the basal ganglia. Overall image quality was good and would be acceptable to readers in clinical practice.

There was no image interpretation instructions included with the submission, or elsewhere in the NDA submission. The clinical team attempted to interpret each patient's image set as positive or negative depending on positron emission signal in the caudate and putamen bilaterally. Any loss of positron emission signal was interpreted as positive. The clinical team then compared its interpretation with the submitted image interpretation determined in the clinical study. The clinical team largely agreed with the submitted image interpretation, although there are several borderline cases in which the clinical team did not fully agree with the image interpretation provided by the applicant.

Special Government Employee (SGE) consultation

The clinical team identified two imaging expert as Special Government Employee (SGE) to independently review the submitted FDOPA PET images from the clinical study conducted by the applicant. The two Special Government Employees were Dr. Henry Royal of Washington University and Dr. Peter Herscovitch of the National Institutes of Health (NIH).

Dr. Royal was first contacted and sent CD-ROMs containing FDOPA PET images of all 45 patients, the image interpretation list submitted by the applicant and the following discussion questions:

1. *Please comment on the likelihood of an ability in practice to discriminate between "positive" and "negative" patients based on these images. Please mark each image as adequate or inadequate for interpretation.*

2. *Please comment on the spectrum of difficulty in interpreting the provided images and provide a binary assessment of diagnostic confidence in interpreting each image.*

3. *Do you agree with the submitted interpretation of the provided images?*

4. *In your clinical judgment, what would be possible clinical utility of FDOPA if it were approved? To the best of your understanding, does it have any known or theoretical advantages or disadvantages as compared to the imaging drug already marketed in US for a similar indication?*

After receiving the FDOPA PET images, Dr. Royal brought up the following question: Was there a formal training program for the blinded readers and, if so, can he have an access to it as well? In other words, were there image interpretation instructions written down some place as to what constitutes a positive or negative image?

The clinical team actually had similar questions when reviewing the submitted FDOPA PET images. How much of a reduction is "reduction"? What if just one caudate has slightly reduced signal?

Subsequently, the 2nd SGE, Dr. Peter Herscovitch, also had the same question: does the NDA specify how the images should be read, and what are the characteristics of an abnormal scan?

Since the NDA submission did not address these questions, a clinical information request was sent to the Applicant on June 10, 2016:

1. *In reference to the three blinded readers who have interpreted the FDOPA images, was there any training provided to them prior to the reading sessions?*

   - *Was there a reading charter?*
   - *Were there any training images?*
   - *If the answer is yes to any of these three questions above, please provide details.*

2. *In reference to image interpretation, are there any specific instructions which would help a reader identify an image as positive or negative? The proposed labeling speaks of "* (b) (4) *" as indicative of an abnormal image. Does it include any* (b) (4) *? Can you be more specific?*

The applicant responded on the same day:

> *"The readers have the tool to convert the DICOM images to a single combined image of the region using 4 to 5 slides. This single slide will clearly demonstrate the condition of the caudate and putamen for interpretation. It will clearly show the loss of dopaminergic neurons if any in these regions for easy interpretation. Any center can get this program from* (b) (4) *etc. and can make it user friendly. That is what we have done.*
>
> *1) There was no training for the readers and is not required*

2) *There was no reading charter*

3) *There is no specific instruction to read the scan, but one has to have the computer program to convert the DICOM images to a single slide for interpretation."*

Reviewer's comments: the applicant probably calls each axial slice through the basal ganglia as a 'slide'.

The Applicant also stated that 99% of the time, only the single-image was read and there was no need for the DICOM. The Applicant explained that the images were read by looking at the combined scan (the single image generated by the "program") and assessing the shape and size of the putamen and caudate to see any loss of dopaminergic neurons. The Applicant confirmed that the procedures as to how the images should be read by the practitioners, or by the 3-blinded readers, were not included in the NDA re-submission dated 12/15/15. Two of the readers were neurologists and the third reader was Dr. Dhawan, a physicist. The applicant stated that in his institution, the FDOPA PET images are read by Dr. Dhawan and the neurologists. Nuclear Medicine or Radiology physicians are not involved in reading the images. The images are read by looking at the composite single image through basal ganglia and assessing the shape and size of the putamen and caudate to see any loss of dopaminergic neurons.

On Monday, June 13, 2016 the FDA review team and the applicant held a teleconference, during which the applicant stated that the patients were referred for imaging by a neurologist and afterwards, Dr. Dhawan or Dr. David Eidelberg would contact the referring neurologist with the image interpretation.

Reviewer's comments: Therefore the applicant confirmed that FDOPA PET image interpretation results were conveyed to the referring physician, who then during follow-up visits, would make a final clinical diagnosis of the patient. This follow-up clinical diagnosis therefore was made by the referring physician who incorporates FDOPA PET imaging results. Since the final follow-up clinical diagnosis was used as the standard of truth in the study, the standard of truth was biased with the FDOPA PET results. This was previously uncovered and discussed (see clinical review document dated 04/22/2016), but is now solidly confirmed by the applicant. This bias in standard of truth is a major deficiency of the clinical study.

It should be noted that the 'clinical study' was conducted under expanded access IND with a request to charge. So the 'study' follows more of the clinical practice rather than be strictly controlled in a typical clinical study setting.

During the teleconference, the FDA asked again what is meant by (b) (4) One reader, a neurologist, described his FDOPA PET image interpretation procedure, during which he systematically reads through all the axial images plus the composite single image through basal ganglia.

Weakness identified during the review of the Major Amendment

Since there was no predefined image interpretation definition, and there was no reader training, FDOPA PET image interpretation procedure in the study appears to be up to each reader. During a teleconference with the applicant, one of the neurologist readers discussed his FDOPA PET image reading methodology which is very systematic and he looks through all of the axial FDOPA PET images. Dr. Chaly (a chemist), on the other hand, in his official response to FDA information request, stated that readers mostly rely on the single composite image through basal ganglia.

Reviewer's comments: The reviewer suspects that of the 3 readers, reader(s) less knowledgeable in neuroanatomy (e.g. the physicist reader), likely relies mostly on the single composite image, as stated by Dr. Chaly. Given that this is a single center study, it is unclear whether the procedure to make this single composite image is standardized across different imaging centers.

Of note, this 'clinical study' (study #17) was conducted under expanded access IND with a request to charge, rather than in a strict clinical trial setting. Therefore the FDA review team did not comment on the lack of an image interpretation charter or a lack of standardized reader training, when approving the expanded access IND with a request to charge in June 2012.

It is also noted that the image interpretation results are largely consistent among the three readers. Therefore the lack of predefined image interpretation definition and a lack of reader training apparently did not significantly compromise inter-reader consistency

Discussion and Recommendation

Overall, the most serious deficiency was the bias of the standard of truth by results of FDOPA PET. This was uncovered during the previous review (see clinical review dated April 22, 1016) and was further confirmed during the review period of the major amendment.

As noted in the reviewer's previous clinical review dated April 22, 2016, a substantial percentage of study subjects (20% overall) did not have the standard of truth (final clinical diagnosis pending or not available). This is worse in subjects with a negative FDOPA PET, in which only about 50% of the subjects have a final clinical diagnosis (SOT).

On the positive side, during the 3 month review period of the major amendment, Good Clinical Practice (GCP) inspection was completed and was found to be satisfactory. The same person who conducted the inspection for the original submission followed up on all original findings at the current inspection for this resubmission.

During 3 month review period of the major amendment, the FDA 505(b)(2) committee also discussed the application. The applicant submitted literature in the original submission of October 22, 2012, and did not submit additional literature in the resubmission of December 15, 2015 (the resubmission contained clinical data obtained by the applicant). The review team considered the submitted literature inadequate to support clinical efficacy. However, the submitted literature was found to be able to support nonclinical and clinical pharmacology aspects of FDOPA.

The chemical structure of FDOPA (fluorodopa) is nearly identical to that of levodopa. Although fluorodopa is a new chemical entity (NCE) due to the presence of the Fluorine atom, its structural similarity to levodopa confers a nearly-identical clinical pharmacology and toxicology profile. No clinical pharmacology studies were conducted by the applicant. The primary information for clinical pharmacology review has been derived from the fourteen publications submitted in the original application. Because fluorodopa (FDOPA) is a small molecule and the administered formulations (those in the literature and the one by the applicant) are (b) (4) solutions, the formulations used in the publications will result in the same clinical pharmacology as the applicant's drug product. Therefore the published literature provides adequate information on the clinical pharmacology of FDOPA to support the NDA. The published literature has been also found to be adequate to satisfy nonclinical pharmacology/toxicology requirements of the application.

This application presents a difficult regulatory decision. On one hand, the applicant complied with FDA recommendation to conduct a clinical study, and literature data support mechanisms of the drug at least from the perspectives of pharmacology/toxicology and clinical pharmacology as discussed above. On the other hand, the clinical study conducted by the applicant has serious deficiencies, particularly the bias in the standard of truth. In addition, supporting data on the performance characteristics of FDOPA PET negative patients are very limited. Overall suggest Complete Response for the applicant to at least collect additional data on FDOPA PET negative cases.

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/s/

BRENDA Q YE
09/06/2016

ALEXANDER GOROVETS
09/06/2016

Summary Review for Regulatory Action

Date	September 5, 2016
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA **Supplement #**	200655 Class 2 resubmission with major amendment
Applicant Name	Feinstein Institute for Medical Research
Date of Submission	December 15, 2015
PDUFA Goal Date	September 15,2016
Proprietary Name **Established (USAN) Name**	None Fluorodopa F 18
Dosage Form **Strength**	Injection 0.42-8.33 mCi/ml
Proposed Indication	For use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected Parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.
Recommended Action for NME	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Ye MD
Statistical Review	Satish Misra PhD, Jyoti Zalkikar PhD
Pharmacology Toxicology Review	Sally Hargus PhD
CMC Review	Martin Haber PhD, Eldon Leutzinger PhD
Microbiology Review	Robert Mello PhD
Clinical Pharmacology Review	Christy S. John PhD
OSI/DCCE	Jong Lee MD
CDTL Review	Alex Gorovets MD
OSE/DRISK	Mona Patel PharmD
OSE/DMEPA	Michelle Rutledge PharmD

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
CMC=Chemistry Manufacturing and Controls
DRISK=Division of Risk Management
DCCE=Division of Clinical Compliance Evaluation
DMEPA= Division of Medication Error Prevention and Analysis

Reference ID: 3981851

1. Introduction

Recommendation for Regulatory Action

On December 15, 2015 the Feinstein Institute for Medical Research submitted this 505(b)(2) NDA application for Fluorodopa F 18 Injection, a radioactive diagnostic agent for use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adults with suspected Parkinsonian syndromes. The present submission for this new molecular entity (NME) is in response to an FDA complete response action taken on October 22, 2013.

The objective of this review is to summarize the recommendation for a Complete Response (CR) action reached by the Division of Medical Imaging Products. The signatory authority for the action for this NME is the Office of Drug Evaluation IV in the Office of New Drugs in the Center for Drugs Evaluation and Research.

Regulatory history of Fluorodopa F 18

Fluorodopa F 18 is a radiopharmaceutical for PET imaging. Historically fluorodopa F 18 was produced in the US in compliance with United States Pharmacopeia (USP) PET compounding standards and monographs and under licensure by the Nuclear Regulatory Commission (NRC). Fluorodopa F 18 was legally marketed for clinical use in positron emission tomography (PET) imaging of neurologic and oncologic conditions. The applicant (Feinstein Institute) has legally produced fluorodopa F 18 and used the drug in clinical practice at the North Shore University Hospital Center for several years.

At a July 28, 2000 public meeting FDA and the Institute for Clinical PET held an informal discussion of the scientific literature for fluorodopa F 18. The meeting concluded that available literature data for fluorodopa F 18 were insufficient to support efficacy in any patient population. It was decided that further discussion of fluorodopa F 18 at an FDA advisory was not warranted at the time.

The more recent legislative history of fluorodopa F 18 and other PET drugs in clinical use begins with the determination by FDA that approved applications for PET drugs are required because these drugs are not deemed generally recognized as safe and effective under section 201(p)(1) and (p)(2) of the Federal Food, Drug, and Cosmetic Act.

On December 9, 2009 FDA issued regulations establishing current good manufacturing practices (cGMPs) for PET drugs. The regulations in 21 CFR Part 212 apply to the production, quality control, holding, and distribution of new PET drugs. The publication of these procedures triggered the implementation timeline specified by the 1997 FDAMA. At the request of drug manufacturers, FDA extended the timeline until June 12, 2012. After that date any facility wishing to continue to produce PET drugs for clinical use was required to have submitted an NDA, an ANDA or to be producing the drugs under an IND. All PET producers must be operating under an approved NDA or ANDA, or effective IND, by December 12, 2015.

On October 30, 2009 the applicant submitted the initial marketing application for fluorodopa F 18. FDA refused to file the application because of inadequate clinical, nonclinical, and CMC data. Notably the NDA did not appear to contain data from adequate and well-controlled studies. FDA acknowledged that many patients had received fluorodopa F 18 injection at the applicant's clinical site. FDA encouraged the applicant to summarize the safety and diagnostic efficacy data from that experience.

The application reviewed in the first review cycle was submitted on October 22 2012. FDA took a Complete Response action on October 22, 2013 because of deficiencies in product quality, clinical, statistical, and good clinical practice.

FDA encouraged the applicant to submit an expanded access IND with a request to charge for fluorodopa F 18. FDA allowed the expanded access IND to proceed and granted the request to charge on June 21, 2012.

Fluorodopa F 18 was first approved for marketing for clinical use in 2010 in France and subsequently in the European Union through mutual recognition under the "well established clinical use" procedure (see previous reviews for details).

Ioflupane I 123

Ioflupane I 123 (DaTscan) is a radiopharmaceutical for Single Photon Emission Computed Tomography (SPECT) imaging approved in the US in 2011 as an adjunct to other diagnostic evaluations in adults with Parkinsonian syndromes (PS) for differentiating essential tremor from tremor due to PS. Ioflupane I 123 targets the dopamine transporter and the resulting image is similar to the image produced by fluorodopa F 18.

2. Background

Fluorodopa F 18 is chemically similar to dopamine and like dopamine it is taken up by dopaminergic neurons. Parkinsonian syndromes are characterized by diminished striatal dopamine uptake principally due to loss of dopaminergic neurons. Fluorodopa F 18 uptake and retention can be visualized in a PET image and might be useful in the evaluation of patients suspected of having a Parkinsonian syndrome.

3. CMC

I concur with the recommendation for approval made in the integrated quality review performed by Dr. Leutzinger. The major chemistry manufacturing and control issues in the NDA included the specifications for the chiral precursor, drug product specifications, data for stability at low pH, validation data for the HPLC purity test and for the bacterial endotoxin assay. These deficiencies have been addressed in this submission.

I concur with the overall Office of Compliance recommendation for approval based on the acceptable inspection of the manufacturing site. The previous deficiencies related to current good manufacturing practices, standard operating procedures, and various product specification issues have been resolved.

FDA expects a shift from research to GMP-grade drug product precursor to occur after an eventual the NDA approval. The agreement under this commitment would be fulfilled within one year after an eventual NDA approval.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology and toxicology reviewer Dr. Sally Hargus that there are no outstanding pharmacology or toxicology issues that preclude approval of this application. Dr. Hargus deferred review of the labeling. The applicant did not submit any original nonclinical data and Dr. Hargus determined that no original data were required.

5. Clinical Pharmacology/Biopharmaceutics

I concur with the assessment of the clinical pharmacology reviewer Dr. Christy John that pending revision of the labeling, there are no major clinical pharmacology issues that preclude approval of this application.

Dr. John does note that in the present application the recommended dose of fluorodopa F18 Injection is (b) (4) 5 mCi. However, in study 17 a dose ranging between 4 and 5 mCi was used. There are no data provided in support of the proposed range and the potential for a non-diagnostic scan exists with the lower dose. Therefore, Dr. John's initial finding that a mass dose of approximately (b) (4) mg and a radioactive dose of 5 mCi are supported by a review of publications remains unchanged.

The reviewer also evaluated the Applicant's measurements of signal intensity in the striatum (diagnostic target) compared to the intensity in the occipital cortex (background) in the patient's scans in study 17. Calculation of the striatal-occipital ratio of signal intensity showed that on average, the signal differed as a function of disease. However, there was considerable overlap between the ratios in positive and negative scans and the measurement is therefore not useful for interpretation of scans in individual patients. I agree with that assessment.

The current submission contains no new information on drug metabolism, drug interactions, or specific populations and none are needed.

6. Clinical Microbiology

This section is not applicable to this NDA. No clinical microbiology data were provided and none are needed.

7. Clinical/Statistical-Efficacy

I concur with the unanimous recommendation by the statistical review team (Drs. Misra and Zalkikar with concurrence by Dr. Gwise) and with the recommendation made by the cross-discipline team leader (Dr. Gorovets) for a complete response action.

In the previous application, the studies conducted by the Applicant (studies 15 and 16) were gravely deficient (see the previous cycle reviews). ON the other hand, the present application does contain verifiable evidence of fluorodopa F 18 performance characteristics from a new study (study 17). The

study is single-center, single-arm and enrolled 45 patients. The primary efficacy end point was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." Loss of dopaminergic neurons in the striatum was based upon the judgment of three blinded independent readers. The final clinical diagnosis by the referring physician was used as the reference standard. See The CTDL review for details of the patient population studied.

However, as discussed by the primary clinical reviewer Dr. Ye (see review dated April 22, 2016) the new clinical study has important limitations. The sample size is small, the reference standard is subject to bias because the diagnosis was made by the referring physician who was not blinded to the fluorodopa F 18 PET scan results. Moreover for a substantial percentage of study subjects the reference standard of the clinical diagnosis is missing (see patient disposition summary by Drs. Ye and Gorovets). Among the 13 patients with negative scans, only five underwent a clinical follow up and only one of had a final diagnosis at the specified interval of 1 year or more after the scan. Among the patients with a positive scan only 20 had a final diagnosis at 1 year or more after the scan.

I note the initial recommendation (4/22/2016) by Dr. Ye for approval of the application. The recommendation is largely based on the assessment that fluorodopa F18 does what it purports to do i.e. it provides for visualization of the striata. I do not find this argument persuasive because of the risks posed by an incorrect diagnosis. To assess the likelihood of this risk, adequate diagnostic performance data are needed. IT should be noted that the final recommendation by the clinical reviewer was pending at the time of this summary review.

The limitations of the data from study 17 are summarized by the statistical review team and are reproduced here from that review. In this data summary only patients with available reference standard (final diagnosis at specified follow up period) are considered evaluable. The table shows agreement figures for the three clinical protocol readers (NDA readers) and the special government employees readers (SGE readers) that assisted FDA in the posthoc review of the images. If the missing data are imputed using worst case assumptions, the severe limitations of the data (particularly the negative percent agreement) become even more pronounced. The term percent agreement (instead of sensitivity and specificity) is used here because the final clinical diagnosis is considered to be an imperfect standard.

Table 1: Positive and Negative Percent Agreement in Evaluable Patients in study 17

	Positive percent agreement: % of PS patients with abnormal scan. (95% Exact Confidence Interval)	Negative percent agreement: % non-PS patients with a normal scan. (95% Exact Confidence Interval)
NDA reader 1	29/31=94% (79 , 99)	5/5=100% (48 , 100)
reader 2	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
reader 3	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
SGE reader 1	27/31=87% (70 , 96)	4/5=80% (28 , 99)
reader 2	29/31=94% (79 , 99)	4/5=80% (28 , 99)

The inadequacy of the performance data will require that the Applicant obtain the missing follow up information (if possible) and resume enrollment in the clinical study.

8. Safety

I concur with the previous conclusions by the clinical reviewers (Drs. Gorovets and Ye) that fluorodopa F 18 does not pose important safety risks based on the single administration of a small mass dose and a small radioactive dose. The extrapolation to fluorodopa of the clinical safety experience with levodopa seems reasonable.

Dr., Ye summarizes the safety experience in the 45 patients in study 17. Study patients were monitored for any physical discomfort. Patients were followed up with a phone call within 24 hours after the scan to collect information regarding adverse events. Forty-four patients responded. The applicant reports that five patients experienced minor adverse events. The events are judged to be unrelated to fluorodopa F 18.

9. Advisory Committee Meeting

No advisory committee meeting was conducted.

10. Pediatrics

The applicant requested a full waiver of pediatric studies in an amendment to the NDA on January 3, 2013. Dr. Ye and Dr. Gorovets agreed that studies of fluorodopa F 18 would be impossible or highly impractical in pediatric patients because Parkinsonian Syndromes are found mostly in adults. On June 5, 2013, the FDA Pediatric Review Committee agreed with granting a full pediatric waiver.

11. Other Relevant Regulatory Issues

I concur with the assessment by Dr. John Lee of the Division of Clinical Compliance Evaluation that the clinical data provided by the applicant in the present submission are reliable. The single confirmatory study for this NDA was audited at a good clinical practice inspection of the Applicant site. No important deficiencies were identified and a Form FDA 483 was not issued. The overall study conduct appeared GCP-compliant, including oversight of study conduct. All audited data were adequately verifiable against source records and case report forms. The inspection outcome was classified as no action indicated (NAI).

I concur with the assessment by Dr. Patel of the Division of (DRISK) that no REMS would be needed for this product were it to be approved. The Applicant did not propose any risk management activities for Fluorodopa beyond routine pharmacovigilance and labeling.

12. Labeling

No substantive reviews of the labeling were conducted by NDA review team because of the clinical and statistical deficiencies with the application.

I note the review of the prescribing information and the vial and lead shield labels and the recommendation by Dr. Rutledge of the Division of Medication Error Prevention and Analysis

(DMEPA). Consideration of the findings and recommendations by DMEPA is deferred.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

I concur with the recommendations for a complete response action made by the statistical review team and by the CDTL. The present application provides insufficient confirmatory evidence of efficacy primarily due to the small sample size and missing data. Therefore, the test scan's performance (in particular specificity) is not adequately characterized.

As noted previously, the Applicant lacks the resources and personnel with the experience and qualifications to conduct an adequate and well controlled clinical study of fluorodopa F 18. There appears to be little or no interest from other government agencies, professional organizations, or commercial manufacturers for the clinical development of the drug.

- Risk Benefit Assessment

Inspectional findings of the Applicant study site show that the data are reliable. However, important limitations of the clinical study lead to insufficient characterization of the performance of fluorodopa F 18.

During this review cycle the clinical and statistical secondary reviewers reevaluated the collective strength of evidence from the literature. The reviewers reaffirmed the lack of adequate and well controlled studies. As such, substantial evidence of the efficacy of the drug is lacking.

Fluorodopa F 18 does not pose important safety risks based on the single administration of a small mass dose and a small radioactive dose

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

I concur with the DRISK reviewer that at this time no risk management strategy appears to be necessary.

- Recommendation for other Postmarketing Requirements and Commitments

The Applicant agreed on April 14, 2016 to submit a Prior Approval Supplement if the NDA, when re-submitted, is approved. The supplement would provide for a cGMP synthesis of the drug substance precursor. The PMC would be fulfilled within one year of the approval of the NDA.

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/s/

LIBERO L MARZELLA
09/06/2016

Cross-Discipline Team Leader Review

Date	August 1, 2016
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA#	200655 Class 2 Resubmission
Applicant	Feinstein Institute for Medical Research
Date of Submission	December 15, 2015
PDUFA Goal Date	June 15, 2016 extended to September 15, 2016
Proprietary/Established names	Fluorodopa F-18 injection/F-18 Fluorodopa (FDOPA)
Dosage forms / Strength	(b) (4) 5 mCi
Proposed Indication	"For use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic investigations".
Recommended:	*Complete Response*

1. Introduction

This document combines the Cross Disciplinary Team Leader (CDTL) review of the resubmission of the New Drug Application (NDA) 200655 for F18 FDOPA with the clinical review of the major amendment to this application submitted on 4/11/16. The primary clinical review has been filed prior to the arrival of the major amendment. The reviews from other disciplines have been filed by now as well. An addendum to the primary clinical review is pending.

The major amendment was submitted as a response to our Information Request for the PET images obtained in the course of the study conducted by the sponsor in accordance with the Complete Response (CR) recommendations. The CR was issued following the review of the original application in 2013. The PET images were submitted for a review by two Special Government Employee (SGE) consultants as part of the two identical but independent of each other Divisional Assignments. The current review of the major amendment reflects the results of these consultations as well as the information provided by the applicant in response to our additional Information Requests. An overview of any other relevant information, historical or more recent, has also been conducted.

The primary clinical reviewer has recommended an approval pending the results of the SGE consultations. All other disciplines, except Statistics, have recommended approval as well. The inspections of the manufacturing facility and the clinical site, found unacceptable during the first review cycle, have now found no outstanding deficiencies. However, the submitted clinical data, from a statistical standpoint, have been deemed inadequate and insufficient. The current review addresses the differences in conclusions among the review disciplines.

The reference is being made to the 2013 CDTL review of the original 2012 application and to the 2013 CR letter for a detailed account of the deficiencies encountered during the first cycle review and now attempted to be addressed in the current submission.

The applicant proposes the following indication for use of F18 FDOPA: *"For use with Positron Emission Tomography (PET) to visualize dopaminergic* (b) (4) *in the striatum* (b) (4) *adult patients with suspected parkinsonian syndromes (PS).* (b) (4) *Fluorodopa F 18 PET is an adjunct to other diagnostic investigations".*

2. Background

F18 FDOPA is accumulated in striatum and its mechanism of action is well understood. There are non-clinical data supporting the potential usefulness of the drug. Its analogue, levodopa (L-DOPA), is a widely used anti-parkinsonian medication. The PET drug has been used in a variety of human research protocols studying the dopaminergic function of striatum. However there has been a paucity of clinical data addressing its utility and diagnostic performance in a relevant patient population.

F18 FDOPA was one of the PET drugs allowed by the FDA in 2000 to be used without an IND or an approved NDA pending the development of the cGMP regulations governing the production of PET drugs. Back in 2000 FDA has also conducted a literature review of the use of the drug in patients with Parkinsonian syndromes and similar disorders but determined the evidence to be insufficient for finding of safety and effectiveness of the use of F18 FDOPA in these patients.

The current applicant has opened an IND 78861 for the use of F18 FDOPA in Parkinsonian patients and submitted an NDA which FDA has at first Refused to File. The updated and revised application was then submitted and filed in 2012. Following the publication of the PET regulations and guidances, the applicant was allowed to start providing an expanded access to the drug under the IND and was eventually authorized to charge for the drug under the applicable IND regulation.

The prior history of this drug development is presented in a greater detail in the 2013 CDTL review. Of note, (b) (4) .

The clinical and statistical reviews of the original 2012 application emphasized three studies: an unpublished retrospective study conducted by the applicant (study 15; n=185), a published study based on a subset of patients from the same study (study 16; n=27) and a published study comparing F18 FDOPA to DaTscan (study 21; n=28). The submitted data were found to be only exploratory and "not sufficient to provide substantial evidence of effectiveness". The CR letter has recommended, among other things, that the applicant conduct an adequate and well-controlled clinical trial in the intended patient population. It specifically advised the applicant "to obtain a standard of reference (follow up clinical diagnosis) in both Fluorodopa F18 PET

positive patients and Fluorodopa F18 PET negative patients". It further stated that a clinical diagnosis as a standard of reference should be made "at a pre-defined time interval following the Fluorodopa F 18 PET scan".

Since then the applicant has continued with the Expanded Access program under the IND 78861 and attempted to conduct a prospectively designed clinical investigation in accordance with the recommendations of the CR letter. The applicant made one important modification to the pre-specified entry criteria, reducing the required to be present "cardinal signs" of Parkinsonism from two to one (tremor, rigidity, bradykinesia or abnormal gait). This was acceptable to the FDA reviewers.

In the current resubmission, the applicant reports on the experience from this single center single arm investigation (study 17) as a response to the 2013 CR letter. In this summary review, the details of the study design and conduct come from the filed primary clinical review and three statistical reviews (primary, secondary and the addendum) as well as from the application itself and additional information provided by the applicant in the course of the review of the Major Amendment. The study protocol although not found in the current application has been located in the recent annual reports to the IND. The integrity of study conduct has been verified and confirmed by the clinical site inspection.

Going over the current clinical and statistical reviews a word of terminological clarification is in order. The applicant and the clinical reviewer, as well as the 2013 CR letter for that matter, speak of "sensitivity" and "specificity" as the performance measures upon which the efficacy of the F18 FDOPA PET is being assessed. The statistical reviewers appear to prefer Positive Percent Agreement and Negative Percent Agreement, respectively. These are defined in the statistical reviews as follows: Positive Percent Agreement represents the percent of patients with abnormal (positive) FDOPA images among all the patients with a clinical diagnostic reference standard of Parkinsonian Syndrome; Negative Percent Agreement represents the percent of patients with normal (negative) FDOPA images among all the patients with clinical diagnostic reference standard of a non-Parkinsonian Syndrome.

The preference for this terminology appears to be based on the fact that here there is no standard of "truth" per se but rather an agreed upon standard of "reference" (a clinical follow-up at a pre-defined time point, in this case). The claim of "visualization" is also being interpreted as a functional claim, i.e. the test visualizes a loss or no loss of dopaminergic (b) (4) and not a diagnostic claim because no specific diagnosis is being made by the test or verified by the reference standard. It should be noted however that the reference standard here is a group of clinical diagnoses which is used to verify the test and collectively can be thought of as a "diagnosis". Regardless, an important precedent has been set in the DaTscan label, (b) (4) while using the terms like positive and negative percent agreements as measures of clinical efficacy.

Whether, in accordance with the 21CFR315 regulations, "visualization" is interpreted as a functional or a diagnostic claim, a clinical follow-up, from a terminological standpoint, is a standard of reference (and has been referred to as such in the 2013 CR letter). For the purposes

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of this review, we accept the statisticians' terminology for the efficacy measures while recognizing that "sensitivity" and "specificity" written in quotations might be more understandable to a clinician.

3. CMC/Device

A number of CMC deficiencies have been identified during the first review cycle and the following items were included in the 2013 CR letter: (1) the absence of a CGMP supply of the precursor (b) (4), (2) absence of a test for chirality of drug substance precursor, (3) absence of justification for non-USP conforming product pH, (4) need for finalization of the specifications for the drug product, and (5) absence of validation of the drug product HPLC chiral identity and purity. The resolution of all these issues has been summarized by Dr. Leutzinger in the 4/19/16 Integrated Quality Assessment.

It is noted that implementation of the shift from research to GMP-grade precursor would not take place until after the NDA approval which has resulted in a Post-Marketing Commitment (PMC). The agreement under this PMC is expected to be fulfilled within one year from the NDA approval. The remainder of the CMC issues has been resolved. Product microbiology issues as well as the facility issues have been all resolved as well. From the product quality standpoint the recommended action is approval.

4. Nonclinical Pharmacology/Toxicology

There were no Pharmacology/Toxicology issues in the CR letter. The recommendation back then was approval. No new nonclinical data have been provided in the resubmission. The current recommendation is approval.

5. Clinical Pharmacology/Biopharmaceutics

The original application was acceptable from the Clinical Pharmacology perspective. In the resubmission, Study 17 has provided quantitative imaging data which were reviewed. As summarized in the review, in addition to visual image interpretation, the applicant assessed Striatal-Occipital Ratio (SOR) which is the ratio of radioactivity in the striatum to that of the occipital cortex used as a background. The reviewer's analysis of the data shows that because there is considerable overlap between SORs in patients with Parkinson's and non-Parkinson's SOR cannot be used as an aid to image interpretation.

The Clinical Pharmacology reviewer also notes that the dose used in Study 17 is 4.05 to 5 mCi and recommends the latter to be the labeled dose. The overall recommendation is approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

Study 17 (see section 2 – Background above) enrolled 45 patients with clinical evidence of a movement disorder and an inconclusive diagnosis of a Parkinsonian or a non-Parkinsonian Syndrome (PS vs. NPS) who were referred for FDOPA PET imaging. As part of the pre-specified clinical protocol the images were read on-site by three independent readers blinded to clinical data. The interpretations were binary (PS vs. NPS) based on normal vs. reduced visualization of striatum. Exploratory quantitative assessments of Striatal Occipital Ratio (SOR) were also performed. In addition, images were separately read at a different time point by one of the readers for the purposes of patient care. With an exception of one patient there were no disagreements among blinded readers or between blinded and clinical reads.

For each patient, the clinical FDOPA PET image interpretation was communicated to the referring physician whose follow up clinical evaluation served as a standard of reference (somewhat incorrectly referred to by the applicant as a "standard of truth"). The protocol called for a clinical follow up assessment at a 1 to 2 year interval after PET imaging. PS diagnoses on clinical follow up included Parkinson's disease (PD), multiple system atrophy (MSA), Gait Freeze, Cortical Basal Ganglion Degeneration (CBD), Pisa Syndrome, and progressive supra-nuclear palsy (PSP). NPS diagnoses included essential tremor (ET), Dopamine Responsive Dystonia (DRD), "Subject without Evidence of Dopaminergic Deficit" (SWEDD), and "no-PD".

Out of 45 patients, 32 had images interpreted as PS and 13 as NPS. In 30 of 32 patients with reduced visualization of striatum, i.e. with images positive for PS, the standard of reference was also recorded as positive for PS and in two the follow up was missing. Out of 13 patients with negative images, seven were lost for follow up, five were recorded as NPS by clinical follow up and one was recorded as PS (a false negative). According to this breakdown there were no false positives.

The clinical review team had a concern about the interpretability of the images used by the applicant for the efficacy assessment and requested the submission of images for further review. The purpose was not to re-adjudicate the results but rather to assess reader confidence and image quality. Given a very small database the team wanted to assess how representative these images were of the ones that would be obtained and interpreted in practice.

At that point in the review process, the primary clinical reviewer, pending the results of the SGE consultation (see below), was recommending an approval, based on the understanding that the applicant, on the face of it, appeared to have followed the FDA recommendations in carrying out the clinical investigation. The primary statistical reviewer while expressing certain concern about data limitations was commenting that the drug might still have some clinical utility. The secondary statistical reviewer has advised against the approval finding the submitted data to be insufficient for adequate assessment of effectiveness and recommended that the applicant continue with the data collection.

In response to the FDA request the applicant has submitted de-identified images from all 45 patients to the NDA, black and white, in the standard format. In addition, color images obtained with the use of a display program that combined several slices into one image of

striatum were submitted along with the list of patient by patient image interpretation by each of the three blinded readers. These were sent along with a Divisional Assignment to each of the two independent Special Government Employee (SGE) consultants, both members of MIDAC (Medical Imaging Drug Advisory Committee), Dr. Henry Royal of Washington University and Dr. Peter Herscovitch of the NIH. Both are well known Nuclear Medicine physicians. Neither one was aware of the other's participation. No clinical data were available to either SGE. Of note, (b) (4)

The following questions were included in the Divisional Assignment and are accompanied here by the responses (the details can be found in the respective minutes):

1. *Please comment on the likelihood of an ability in practice to discriminate between "positive" and "negative" patients based on these images. Please mark each image as adequate or inadequate for interpretation.*
   Dr. Royal found all images to be adequate with color images being less optimal than the black and white. It was easy to tell apart negative from positive.
   Dr. Herscovitch found all images easy to read in black and white and has not assessed color images at all. He characterized them all as adequate.

2. *Please comment on the spectrum of difficulty in interpreting the provided images and provide a binary assessment of diagnostic confidence in interpreting each image.*
   Dr. Royal felt that the spectrum of difficulty was reasonable and was confident in assessing every image.
   Dr. Herscovitch rated diagnostic confidence on a scale from A to D. The majority (34) were ranked as A, six as B, and five as C.

3. *Do you agree with the submitted interpretation of the provided images?*
   Dr. Royal disagreed with interpretation of images in four patients (two positive and two negative).
   Dr. Herscovitch disagreed in five cases all of which he considered to be positive whereas the on-site blinded readers interpreted them as negative. (Of note, in none of these five a pre-defined standard of reference is available for our review).

4. *In your clinical judgment, what would be possible clinical utility of FDOPA if it were approved? To the best of your understanding, does it have any known or theoretical advantages or disadvantages as compared to the imaging drug already marketed in US for a similar indication?*
   Dr. Royal thought the clinical utility would be similar to that of DaTscan with PET (FDOPA) most likely resulting in a better image resolution that SPECT (DaTscan).
   Dr. Herscovitch also thought the utility would be similar. FDOPA would not need thyroid blocking although it does require premedication with a single dose of carbidopa. Acquisition time would be shorter and radiation dose somewhat smaller with FDOPA. Resolution would be better with FDOPA but the significance of this could be hard to judge without comparing the performance data. A theoretical concern was raised about a potential under-diagnosing of an early PD by FDOPA because of a metabolic up-regulation.

During the discussions with the SGEs the issue of reader training was raised and further clarified with the applicant in the subsequent telephone conferences. It was confirmed that there was no reader training and no imaging charter. The three independent blinded readers in Study 17 were a medical physicist and two neurologists, all with many years of experience in reading FDOPA scans. Although it was considered somewhat problematic that no Nuclear Medicine physicians were involved in Study 17, the clinical team felt that any adequately trained radiologist or a Nuclear Medicine physician should be able to read these images, a view supported by the SGEs. The image interpretation instructions were also further reviewed in the follow up discussions with the applicant.

In addition to clarifying the issues surrounding image interpretation the clinical team queried the applicant on the issue of the standard of reference (or "truth"). The applicant has confirmed that the FDOPA image interpretation was indeed available to a clinician providing the follow up assessment against which the ability of the test to visualize the neuronal loss or no loss was being measured. Given the obvious concern with a possible bias the issue of the time interval between the imaging test and the follow up clinical assessment has again come up and is illustrated in the Table 2 of the Addendum to the Statistical review.

Upon further review it appears that only one out of 13 patients with negative images had a clinical follow up at the pre-defined time interval of one year or longer. One had it at 11 months, one at 3 months, one at three weeks, one at two weeks, one at one week and seven had no known follow up at all. Out of 32 patients with positive images, only 20 had a standard of reference obtained at 1 year or more following the F18 FDOPA PET.

In view of this data deficiency both clinical and statistical review teams have determined that the resubmitted application is not adequate for approval. (At the time of this memo filing, the addendum to the primary clinical review has not been completed yet.)

In addition to the review of the resubmitted application the clinical and statistical reviewers have reexamined the literature based evidence. The internal 2001 divisional package with the literature review was re-reviewed but no new evidence found. Although there were over 500 publications at the time of the original review including 60 clinical studies in patients with movement disorders, none were considered adequate and well controlled and none involved image interpretation by independent readers blinded to clinical data. The search of a more recent literature revealed no new publications since the 2012 review submitted in the original application by this applicant, except for a small (n = 28) single center retrospective study identified by the current review team (N. Ibrahim et al: The sensitivity and specificity of F-FDOPA PET in a movement disorder clinic, American Journal of Medical Molecular Imaging 2016; 6 (1): 102-109). The readers here again were not blinded to clinical data and clinicians were not blinded to the imaging data, however the patients were followed clinically for at least two years and the clinical follow up served as a standard of reference. Twenty patients with positive images were verified to be clinically positive for a Parkinsonian syndrome. Seven negative images were clinically negative and one was false negative.

8. Safety

No new safety concerns have been identified during the review of this resubmission.

9. Advisory Committee Meeting

There was no AC meeting. The SGEs were consulted as described above.

10. Pediatrics

Pediatric waiver has been granted during the review of the original application as PD does not occur in children.

11. Other Relevant Regulatory Issues

No data integrity or study conduct issues have been identified during the clinical site inspection. The sponsor again has submitted a waiver of the new drug exclusivity.

12. Labeling

In view of the planned Complete Response no labeling review has been conducted.

In response to the Information Request earlier on the review process the sponsor has updated the Dosimetry table which might still have to be finalized during an eventual labeling review.

13. Recommendations/Risk Benefit Assessment

The CDTL recommendation is to issue a CR to this resubmitted F18 FDOPA application.

Insufficient clinical follow up in Study 17 is the main deficiency in this re-submitted application for the use of F18 FDOPA PET in patients with suspected Parkinsonian syndromes. (b) (4) , no substantial evidence of effectiveness has been demonstrated to assess the drug's benefit. Although there are no safety issues with the use of this drug, the risk of misdiagnosis cannot be adequately assessed either.

To summarize, out of 45 patients, 21 patients were followed for over 1 year and provided adequate data for efficacy assessment. One patient had an NPS diagnosis on the standard of reference determination and an FDOPA image interpretation consistent with NPS. This would give a negative percent agreement (or "specificity") of 100% with the lower bound of 95% CI of only 2.5% which is unacceptable. Twenty patients had a standard of reference diagnosis of PS and an FDOPA image interpretation of PS. This gives a positive percent agreement ("sensitivity") of 100% for all three readers with a 95% CI: (83%, 100%), according to additional calculations performed by Dr. Zalkikar.

The above measurements have been carried out on the "evaluable" patients only. If one were to use an "intent-to-diagnose" population and impute as wrong some or all of the imaging data based on missing reference data for patients with negative images (resulting in high false negatives) the "sensitivity" estimate would decrease with a significant drop in the lower bound of the 95% CI. It should be noted that at least one of the two SGEs disagreed with the five negative image interpretations in whom there were no standard of reference, so these could have easily become all false negatives depending on the standard of reference determination.

Although there is a good understanding of this drug's mechanism of action and a reasonable expectation that it should image what it purports to image there are still no adequate confirmatory clinical data available. Whereas an investigational use can be allowed to continue it would be premature to approve the drug for marketing. The current applicant has a long standing history and experience with the use of F18 FDOPA in patients with suspected movement disorders and whether this applicant would produce the drug for distribution to others is unclear.

While not directing bearing on the decision to approve or not to approve, it should be also noted that with the exclusivity waived and generic drug development possible it would be inappropriate to approve the current application without adequate performance data. The latter consideration is particularly relevant given the availability in this country of an approved product (DaTscan) for which the performance data for the same indication are available.

In the current resubmission the applicant has also provided the available European labels for F18 FDOPA. The issue of European approvals has been covered in the 2013 CDTL review and there are no review updates at this time.

It is unfortunate that in spite of its prospective design Study 17 has been terminated prematurely and thus incomplete data have been submitted for our review and analysis. We therefore recommend that the applicant continue collecting data on the patients enrolled so far and enroll additional patients for further analyses as pre-specified in the protocol. We would also encourage the applicant to contact us for planning an appropriate statistical analysis of the collected data.

Our preliminary estimation at this time is that the applicant would have to altogether enroll at least five to six patients with a negative reference standard, pre-defined as a clinical follow up over one year. The required number of patients with a positive reference standard might depend on the amount of missing data among patients with negative images (these projections have not been formally confirmed by the statistical review team).

Here are the draft comments to the applicant:

Clinical/Statistical:

Your resubmitted application contains the report of the prospectively designed "Study #17" conducted by you following the previous Complete Response issued by us on 10/22/13. We have identified the following deficiency:

In the Study #17 you have imaged 45 movement disorder patients with F18 FDOPA PET. Of these patients, 32 had images interpreted as positive for visualization of a loss of dopaminergic neurons in striatum and 13 as negative. Out of these 13 patients only five had undergone a clinical follow up which was supposed to serve as a standard of reference and only one of these had a clinical follow up at a pre-defined time interval following the F18 FDOPA PET (> 1 year). Some patients had an interval as short as one or two weeks. Therefore, out of 13 patients with no loss of dopaminergic neurons in striatum as visualized on the F18 FDOPA PET only one had this interpretation adequately verified.

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This is not acceptable especially in view of the availability of the image interpretation to the clinician providing the follow up. Such a standard of reference is not adequate for the proposed visualization claim.

We also note that in patients with "positive" images only 20 had a standard of reference obtained 1 year or more following F18 FDOPA PET. This is also inadequate.

To address this deficiency we recommend that you obtain the clinical follow up at a minimum of 1 year after the imaging test for the patients you have already enrolled and extend the Study #17 to enroll additional patients who will also go on to have a clinical follow up at a pre-defined interval as an adequate standard of reference.

We also recommend documenting clearly, at follow up, which clinical features in each patient were consistent with Parkinsonian or Non-Parkinsonian syndrome.

We invite you to seek a meeting with us to design an appropriate Statistical Analysis Plan for the completion and extension of the Study #17.

Additional Comments – Quality:

We remind you of your 4/14/16 Post-Marketing Commitment (PMC) to submit a Prior Approval Supplement if the NDA, when re-submitted again, is approved. The PMC should be fulfilled within one year of the approval of the NDA. The supplement will provide for a cGMP synthesis of (b) (4), the drug substance precursor, as manufactured by (b) (4) It will contain a complete certificate of analysis for the precursor demonstrating equivalence with previously used clinical material. In addition, documentation will be provided on the following (b) (4) The starting material for the GMP synthesis will be (b) (4), with appropriate specifications. Please note that approval of this supplement may require an inspection of (b) (4).

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/s/

ALEXANDER GOROVETS
08/16/2016

CLINICAL REVIEW

Application Type	New Drug Application Class 2 Resubmission
Application Number(s)	200655
Priority or Standard	Standard
Submit Date(s)	December 15, 2015
Received Date(s)	December 15, 2015
PDUFA Goal Date	June 15, 2016
Division/Office	Division of Medical Imaging Products/ODE IV
Reviewer Name(s)	Brenda Ye
Review Completion Date	April 22, 2016
Established Name	Fluorodopa F-18 Injection
(Proposed) Trade Name	Fluorodopa F-18 Injection
Applicant	THE FEINSTEIN INSTITUTE FOR MEDICAL RESEARCH
Applicant Proposed Indication(s)/Population(s)	Used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected Parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.
Recommendation on Regulatory Action	Approval pending Special Government Employee (SGE) consultation and satisfactory Good Clinical Practice (GCP) inspection

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1 Executive Summary

1.1. Product Introduction

Fluorodopa F 18 Injection is a radiopharmaceutical proposed to be used in Positron Emission Tomography (PET) to visualize striatal dopaminergic (b) (4) in patients with suspected parkinsonian syndromes (PS). At the onset of Parkinsonian Syndrome, (b) (4)

Applicant Proposed Indication:

Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes (PS). (b) (4) *Fluorodopa F 18 PET is an adjunct to other diagnostic investigations*.

1.2. Conclusions on the Substantial Evidence of Effectiveness

At least on the surface, the applicant followed the FDA review team's guidance of conducting a new clinical study to address the clinical deficiencies cited in the Complete Response (CR) Letter. The new clinical study (Study #17) has pre-specified clinical protocol and uses follow-up clinical diagnosis of at least one-year as the standard of truth. Data integrity is being investigated with clinical inspection (GCP inspection scheduled, inspection results pending).

However the new clinical study (Study #17) has its own limitations. The final clinical diagnosis (standard of truth) was biased because the final clinical diagnosis was made by the referring physician who received F-DOPA PET imaging results prior to making a final clinical diagnosis, which is used as the SOT of the study. In addition, a substantial percentage of study subjects (20% overall) did not have the standard of truth (final clinical diagnosis pending or not available). This is worse in subjects with a negative FDOPA PET, in which only about 50% of the subjects have a final clinical diagnosis (SOT).

If one looks at all of the submitted clinical studies, in this review cycle or the previous review cycle, the total application package looks a bit stronger. In the previous review cycle, Studies #15/16 conducted by the applicant was found to be gravely deficient. However Study # 21, a literature publication comparing the performance characteristics of FDOPA and DaTscan,

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provided some evidence of efficacy of F-DOPA, even though Study #21 had its own limitations as cited in the Complete Response Letter.

If one looks at only the patient population who have positive F-DOPA PET and exhibit at least one sign/symptom of Parkinsonian syndrome, available data provide some supporting evidence of the efficacy of the FDOPA PET imaging. In this patient population, the FDOPA PET imaging appears to have a fairly high positive predictive value of confirming striatal dopaminergic neuronal loss.

Given that at least on the surface, the applicant followed the FDA review team's guidance and some clinical utility could be found for F-DOPA PET imaging in a selected patient population (patients with positive F-DOPA PET and at least one sign/symptom of Parkinsonian syndrome), the reviewer recommends approval pending Special Government Employee (SGE) consultation and satisfactory Good Clinical Practice (GCP) inspection.

2 Regulatory Background

2.1. U.S. Regulatory Actions and Marketing History

The current submission is a resubmission in response to FDA Complete Response (CR) letter dated 10/22/2013. The FDA Complete Response letter had 6 sections with specific comments:

1 Clinical/Statistical
2 Good Clinical Practice (GCP) Inspection
3 Product Quality
4 Labeling
5 Safety Update
6 Additional Comments

With regard to clinical review, the relevant clinical comments in the CR letter include:

"Your application contains no data from adequate and well controlled clinical trials. Significant deficiencies have been identified in the referenced literature studies and in the studies you have conducted in support of this application. The data submitted in your application are not sufficient for evaluating the diagnostic effectiveness and usefulness of Fluorodopa F 18 PET in the proposed patient population.

1. The following deficiencies have been identified with clinical Study #15, which was conducted at the Feinstein Institute of Medical Research:

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a. The study is a retrospective, single center study.

b. The study was not conducted according to a pre-specified protocol, and hence, definitions of the primary efficacy endpoint and the standard of truth that would normally be specified by a protocol, are not well-defined for the study.

c. The study used each patient's clinical diagnosis at the time of referral for a Fluorodopa F 18 PET scan as the standard of truth for measuring the test's performance characteristics. We do not find such a standard to be clinically meaningful and do not agree with the cited diagnostic performance measurements of Fluorodopa F 18 as 100% for sensitivity and 100% for specificity.

d. Of the 185 study patients, 158 patients had a pre-imaging clinical diagnosis of Parkinson's disease and were responding to Parkinson's disease medications. For these patients a Fluorodopa F 18 PET scan provides no additional clinically useful information. Deficiencies concerning the remaining 27 study patients are discussed below (Study #16).

e. You have provided no documentation that Fluorodopa F 18 PET images have been read independently by three readers blinded to clinical information. Furthermore, inspection of the study site revealed that none of the 47 audited cases contained documentation that each patient's images were read by three blinded readers.

2. Study #16 is a publication with the follow-up results of 27 Fluorodopa F 18 PET negative patients enrolled in Study #15. Study #16 has the following major deficiencies:

a. Per your amendment dated April 5, 2013, only 8 of the 27 Fluorodopa F 18 PET negative patients from Study #15 were followed for 2 to 4 years to obtain the patient's final clinical diagnosis. Clinical data from such a small number of patients do not provide a reliable assessment of the performance characteristics of Fluorodopa F 18 PET. Furthermore, inspection of the study site revealed that none of the subject files contained documentation (clinical follow-up confirmation) of the continued absence of classical Parkinson's Disease symptoms and signs.

b. The reasons for not obtaining follow up on the remaining 19 patients are not provided.

Among the remaining literature publications in your application (Studies #17-23), only the publication by Eshuis et al. (Study #21) provides clinical data for the assessment of the efficacy of Fluorodopa F 18 as a diagnostic radiopharmaceutical. However, Study #21 does not provide substantial evidence of efficacy for the following reasons:

a. The study is a small single center study and is exploratory in design.

b. All study patients had a diagnosis of Parkinson's disease at the time of enrollment. The study excluded patients with atypical signs and patients not responding to Parkinson's disease medication. Therefore, the study does not evaluate a patient population that might benefit from a diagnostic imaging test.

c. The definition of positive scans (mean standard uptake value in patients below two standard deviations of the mean in healthy controls) is an exploratory quantitative measure and its threshold is arbitrarily set.

d. It is unclear how specificity was calculated, as all patients included in the analysis of the study had confirmed Parkinson's disease.

To address these deficiencies, we recommend the following:

1. Conduct an adequate and well-controlled clinical trial which might provide substantial evidence of effectiveness of Fluorodopa F 18 in the intended patient population. We encourage you to develop such a study using a pre-defined standard of reference for measuring the performance characteristics (sensitivity and specificity) of Fluorodopa F 18, a pre-specified statistical analysis plan, and image interpretations made by independent readers blinded to clinical information. Note in order to measure the sensitivity and specificity of Fluorodopa F 18, you need to obtain the standard of reference (follow-up clinical diagnosis) in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18 PET negative patients. You should use as a standard of reference the clinical diagnosis made by a movement disorder specialist at a predefined time interval following the Fluorodopa F 18 PET scan.

2. The study population must include subjects who might benefit from the Fluorodopa F 18 PET scan. Such patients could include those in whom Parkinsonian and essential tremor could not be differentiated on clinical grounds, those with suspected early onset of Parkinsonian syndrome, and/or those not responding to a Parkinson disease medication. To facilitate the interpretation of the study's results, we recommend that you consider exclusion of subjects with features suggestive of multiple system atrophy or progressive supranuclear palsy, response to Parkinson's disease medication, a clinical history exceeding five years, and concomitant medication known or suspected of interacting with striatal uptake of Fluorodopa F 18.

3. We reference the Good Clinical Practice (GCP) deficiencies identified during our inspection of your clinical study site and communicated to you on March 22, 2013. These deficiencies call into question the reliability of the clinical data in your application. It is necessary to conduct a study in compliance with GCP standards to ensure the quality and integrity of the data."

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2.2. Foreign Regulatory Actions and Marketing History

Fluorodopa F 18 PET was approved in France in 2010 followed by several other countries in the European Union, including England. Fluorodopa F 18 PET approval in France and other EU countries was based on the clinical study publications alone from the literature, and was not based on any particular clinical study conducted by the pharmaceutical companies who hold the approval for marketing. The application resubmission includes labeling from three manufacturers marketing Fluorodopa F 18 Injection in various EU countries.

3 Sources of Clinical Data and Review Strategy

APPEARS THIS WAY ON ORIGINAL

In response to the FDA Complete Response letter, in which the FDA listed serious design and conduct deficiencies of the previous clinical study (study #15 and #16), the applicant states in the resubmission that since the clinical studies were already completed in the past, nothing could be done to correct the deficiencies in these old studies. Since in the Complete Response letter, FDA suggested a new study to satisfy the deficiencies indicated in the Clinical/Statistical and GCP comments, the applicant conducted a new prospective clinical study under the Expanded Excess IND 78861 for F-18 FDOPA from Feinstein Institute. The study title is "Fluorodopa F 18 PET Imaging for the Differential Diagnosis of Parkinsonian Syndromes" (Study #17). This new clinical study (study #17) is submitted to address the Clinical/Statistical and GCP deficiencies listed in the FDA Complete Response Letter.

4 Review of Relevant Individual Trials Used to Support Efficacy

STUDY# 17: FLUORODOPA F 18 PET IMAGING FOR THE DIFFERENTIAL DIAGNOSIS OF PARKINSONIAN SYNDROMES

4.1.1. Study Design

Overview and Objective

"Study #17" is a prospective single center clinical study conducted at the Feinstein institute under Expanded IND 78861 with a request to charge for F-18 F-DOPA. The main objective of the study was to determine the sensitivity and specificity of Fluorodopa PET in patients suspected of Parkinsonian syndromes. The study title is "Fluorodopa F 18 PET Imaging for the Differential Diagnosis of Parkinsonian Syndromes".

Trial Design

PET scans were evaluated based on the visualization of the size and shape of the putamen/caudate in the striatum. Each patient had a Fluorodopa PET scan to determine the condition of the striatum and the patients were followed up one to two years past the date of their PET scan in order to establish the standard of truth (SOT). In some cases the SOT was received earlier than a year based on the decision by the referring physician.

A total of 45 patients were given Fluorodopa F 18 PET scans. Three independent image readers read the scans to evaluate the shape and size of the putamen/caudate to determine the loss or no loss of dopaminergic neurons. Visual interpretation of the scans were recorded either as positive (loss of dopaminergic neurons) or negative (no loss of dopaminergic neurons).

Enrollment Criteria

Enrollment criteria: Patients with 1-2 signs and symptoms of Parkinsonian syndrome (tremor,

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rigidity, gait disturbance)

Reviewer's comments: Approximately one year after the Expanded Access IND for F-18 FDOPA with a Request to Charge request was granted in June 2012, the applicant requested to relax the enrollment criteria from two signs and symptoms of Parkinsonian syndromes to one sign/symptom of Parkinsonian syndromes, because under the previously set enrollment criteria the study recruited almost no patients in a year. The applicant submitted this request along with an annual renewal for a request to charge under the Expanded Access IND for F-DOPA. The agency granted the requested enrollment change and the charge renewal request.

Inclusion Criteria: All patients in this study were referred by Neurologists and exhibited at least one of the cardinal features of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder).

Reviewer's comments: Another 'enrollment criterion' that was not specified in the protocol but was implemented by the applicant was that only patients who were willing to pay for the FDOPA PET were studied, since the applicant states it has limited funding and resources. The application states that "As indicated to FDA since the Fluorodopa Expanded Access IND was not reimbursed by CMS we had to depend upon patients who are willing to pay for the clinical studies".

Study Drug Dosing

Fluorodopa F 18 Injection (150-185 MBq, 4.05-5.0 mCi) was administered by intravenous injection.

Carbidopa (150 mg) was administered orally to patients approximately 60-90 minutes prior to administration of Fluorodopa F 18 Injection. The optimal dose of 150 mg was determined based on the investigator's own experience as well as other peer-reviewed publications. Other clinical study groups have used lower than 150 mg of Carbidopa to generate well resolved images. A maximum dose of 200 mg was recommended by Bristol Myers Squibb according to the package insert for carbidopa published in September 2006.

Image Interpretation

Three separate onsite readers read the scans to evaluate the shape and size of the putamen/caudate to determine the loss or no loss of dopaminergic neurons. A reduced uptake in the putamen or both putamen and caudate, unilaterally or bilaterally indicates the loss of dopaminergic neurons. The scans were interpreted visually and the results were reported as positive or negative.

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Reviewer's comments: it is unclear whether the readers were blinded. The application describes the procedure as blinded image interpretation, although what was blinded to the readers is not described clearly in the application.

Standard of Truth

The applicant followed the referring physician up to 1 year and in some cases up to 2 years to determine the final clinical diagnosis, which is the standard of truth (SOT). In some cases the SOT was received earlier than one year.

Reviewer's comments: The final clinical diagnosis used as the standard of truth was made by the referring Physician, who also received results of the FDOPA PET from the Feinstein Institute. Therefore, the standard of truth is biased by the results of the F-DOPA PET results.

4.1.2. Study Results

Compliance with Good Clinical Practices

The applicant did not submit a statement attesting that the new clinical study (Study #17) was conducted in accordance with Good Clinical Practice. However, the applicant emphasized in the resubmission that the study was conducted under Institutional Review Board (IRB).

Because of the data integrity issues uncovered during the last review cycle (cited in the FDA CR letter), the review team again consulted the FDA Office of Scientific Investigations (OSI). At the time of the completion of this clinical review, OSI GCP inspection has been scheduled for early May 2016, with the GCP inspection report expected in the ensuing weeks.

Patient Disposition

The total number of patients referred to The Feinstein Institute for this study was 45 (or 46).

Reviewer's comments: It is unclear from the resubmission if the total number of patients referred to the clinical study was 45 or 46. The submission narratives state 45 subjects, but some of the study tables, including the recently submitted patient images suggested 46 subjects.
Out of 45 (or 46) patients, 32 had positive PET scans and 13 had negative PET scans. The applicant was able to obtain the Standard of Truth (SOT) in 30 patients who had positive PET scan results. Two patients who had positive PET scan results have a pending SOT. Out of the 13 negative scans, the applicant was able to collect SOT for 6 patients and the other 7 are pending.

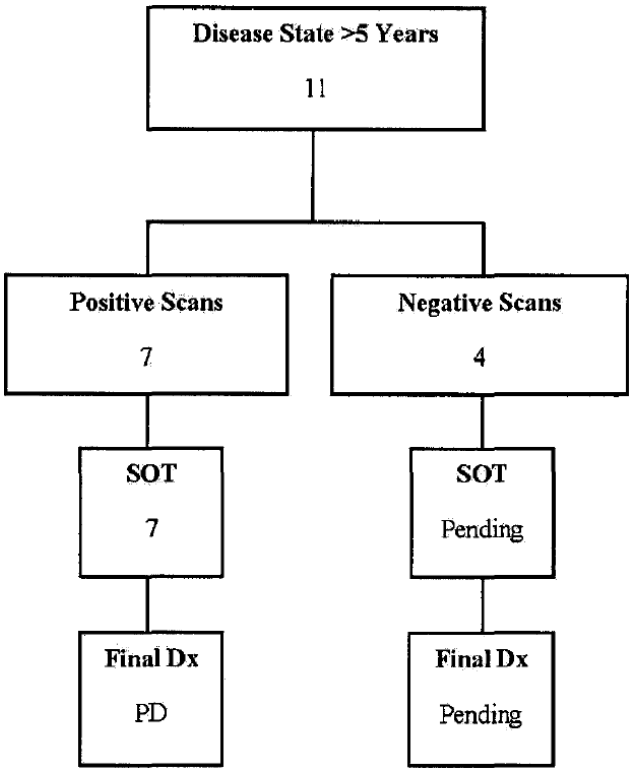
Reference ID: 3921586

The application states that "Out of the 13 negative scans, we received SOT's for 6 patients and the other 7 are pending. We have made several attempts to collect SOT's from the referring physicians for the 7 patients, but were not successful. We will continue our attempts but we are not very confident. It was difficult to collect SOT's from patients with negative PET scans."

Reviewer's comments: The difficulty to collect SOTs from patients with negative PET scans likely reflects the difficulty the referring physician has in making a final clinical diagnosis for patients with negative FDOPA PET, even given a one-year clinical follow-up you period. These are likely patients who exhibited one or more sign/symptoms of Parkinsonian syndrome, but didn't respond to standard anti-Parkinson medication.

Out of the 45 patients, there were 11 patients exceeding 5 years of disease duration. In 11 patients, 7 had a positive PET scan and 4 patients had a negative scan. The applicant obtained final clinical diagnosis (SOT) for all 7 patients who had a positive scan. All four patients with a negative scan have pending SOT's (Figure 1).

Figure 1: Patients with a Disease Duration Exceeding 5 years.



Reference ID: 3921586

Reviewer's comments: Note that out of the seven patients with negative FDOPA PET and pending standard of truth, four of them have disease duration exceeding five years. More than half (4 of 7) of patients with negative F-DOPA PET and pending standard of truth have a disease duration greater than five years. So a longer follow-up period is unlikely to improve the accuracy of the final clinical diagnosis, which is used as the standard truth. It seems that for patients with negative F-DOPA PET, the scan's clinical value to a clinician is limited.

The applicant proposes (b) (4)

Table of Demographic Characteristics

Table 1: Subject Demographics

Variable	Statistics	Overall Subjects n=45	Patients with Loss of Dopaminergic Neurons n=32	Patients with No Loss of Dopaminergic Neurons n=13
Male	n (%)	32 (71.1%)	24 (75.0%)	8 (61.5%)
Female	n (%)	13 (28.9%)	8 (25.0%)	5 (38.5%)
Age	Mean (M) (SD) Mean (F) (SD) Mean (M & F) (SD)	60.34 years (12.44) 54.23 years (14.08) 58.58 years (13.08)	N/A	N/A

Efficacy Results – Primary Endpoint

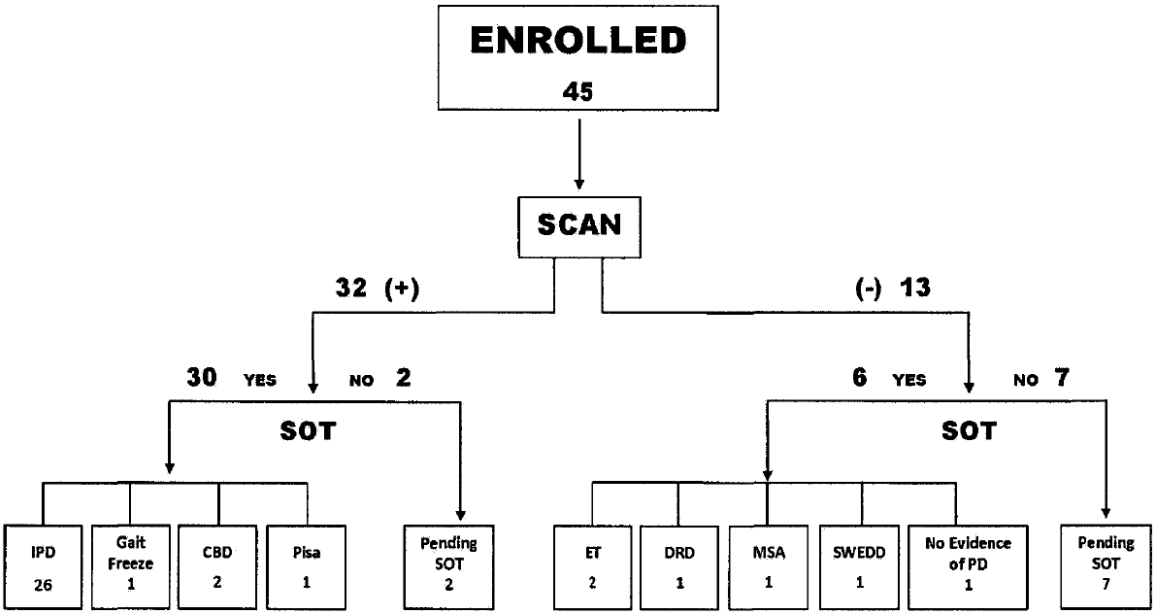
Pre-specified primary endpoints of the study were sensitivity and specificity of F-DOPA PET imaging with final clinical diagnosis as the Standard of Truth (SOT). The accuracy of the calculated sensitivity and specificity relies on the accuracy of the standard of truth. However in this study, the reported final clinical diagnosis (standard of truth) was biased, because the final clinical diagnosis was made by the referring physician, who received results of the FDOPA PET imaging prior to making a final clinical diagnosis. In addition, although the standard of truth was obtained in over 90% of patients with positive FDOPA PET, final clinical diagnosis (SOT) was missing/pending in over 50% of the patients with negative FDOPA PET imaging (Table 2). The reviewer therefore considers the sensitivity and specificity values reported in the resubmission unreliable.

Table 2: Availability of Final Clinical Diagnosis (SOT) in Patients with Positive or Negative FDOPA PET

	FDOPA PET Positive	FDOPA PET Negative	Overall
SOT obtained	30	6	36
SOT pending/not available	2	7	9
Total	32	13	45
Percentage of subjects with missing/pending SOT	7%	54%	20%

Figure 2: Distribution of Final Clinical Diagnosis Based on the Scan Results

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IPD: Idiopathic Parkinson disease
CBD: Cortical Basal Ganglion Degeneration
Pisa: Pisa Syndrome
ET: Essential Tremor
DRD: Dopamine Responsive Dystonia
MSA: Multiple System Atrophy
SWEDD: Subject without Evidence of Dopaminergic Deficit

Efficacy Results – Exploratory Brain Regional Quantitative FDOPA Uptake Analysis

The applicant also conducted an exploratory quantitative FDOPA uptake analysis based on uptake measures in six striatal brain regions: left posterior putamen, right post putamen, left anterior putamen, right anterior putamen, left caudate, and right caudate. Each region's F-DOPA uptake is compared to the uptake of the occipital lobe, which is used as an internal control region. The resulting ratio, the Striatal Occipital Ratio (SOR), is listed in tables below. Table 4 lists SOR values in patients with negative scan. Table 5 lists SOR values in patients with positive scan.

Table 3: Striatal Occipital Ratio (SOR) in FDOPA PET Negative Subjects

Reference ID: 3921586

Subject ID #	Left P Put	Right P Put	Left A Put	Right A Put	Left Caudate	Right Caudate	Scan Results
[redacted] (b) (4)							
Average	2.290	2.254	2.665	2.638	2.634	2.605	
Std Deviation	0.285	0.272	0.310	0.291	0.340	0.219	

Table 4: Striatal Occipital Ratio (SOR) in FDOPA PET Positive Subjects

Subject ID #	Left P Put	Right P Put	Left A Put	Right A Put	Left Caudate	Right Caudate	Scan Results
(b) (4)							
Average	1.678	1.683	2.148	2.137	2.300	2.236	
Std Deviation	0.205	0.218	0.246	0.270	0.220	0.315	

Reviewer's comments: From Table 4 and Table 5, one can see that bilateral posterior putamen is more often affected when there is striatal dopaminergic neuronal loss, as shown by reduced uptake of F-DOPA in the region compared to that of the occipital lobe, the internal control region. On the other hand, the anterior putamen and caudate may remain negative or affected less on F-DOPA PET (F-DOPA uptake not reduced compared to that of the occipital lobe, the internal control region) even when the entire scan is visually read positive and patient's clinical diagnosis is Parkinson Disease. Potentially these regional quantitative measures could be helpful in case the visual image interpretation of the FDOPA PET is border line.

5 Review of Safety

5.1. Review of the Safety Database

Study #17 added 45 patients to the safety database of F-DOPA. In the study, patients were monitored visually for any physical discomfort. After the PET scans, all patients were followed up with a phone call within 24 hours to collect information regarding any possible adverse events. Forty-four patients responded to the phone call.

5.2. Safety Results

In Study #17, there were five cases in which the patients had minor events. In all cases, after discussing with the patients, the Principle Investigator (PI) concluded that the minor adverse events were not caused by the administration of Fluorodopa F 18 Injection.

Minor adverse events collected from the patients within 24 hours (after the PET study) are listed below:

• In one subject, the patient reported mild burning in the throat in the evening of the scan. Based on the discussion with the patient, the PI concluded that the burning sensation was attributed to a pre-existing GERD condition.

• Another patient reported a small bump on the right arm and cheek several hours after the scan. The patient told the PI that the patient has very sensitive skin. The bump on the arm and cheek were gone after several hours. From their discussion the PI concluded that the adverse event was not due to Fluorodopa F 18 Injection.

• One patient had a mild headache in the evening of the scan and experienced left arm tremor for 15 minutes the following day. The PI followed up with the patient and concluded that these events were not related to Fluorodopa F 18 Injection.

Reference ID: 3921586

• One patient reported a bruise and slight swelling 2 days after the scan, possibly at the injection site. The patient consulted with the doctor and the doctor told the patient that it could be due to the IV and these types of events are general risks of IV. There was no infection at the site and the swelling had gone down in a few days. The PI was notified of the report.

• One patient reported feeling "off' and tired since the test. BP was slightly higher than usual. Symptoms were gone by the time the patient was contacted for adverse event reporting. They patient did not seek out medical treatment. The PI concluded that this particular event might be due to cessation of the neupro patch and supplements for the test subject. The PI concluded that the symptoms were not likely related to the scan.

6 Special Government Employee (SGE) Consultation

A Special Government Employee, who is an expert of F-DOPA PET imaging, has been selected to independently review the F-DOPA PET images from the new clinical study (Study #17). At the time of the completion of the clinical review, the SGE is undergoing government clearance process.

Reference ID: 3921586

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/s/

BRENDA Q YE
04/22/2016

ALEXANDER GOROVETS
04/22/2016

Division of Medical Imaging Products (DMIP)
Health Physics Report
General Correspondence re NDA 200655
FDA/CDER/OND/ODE-IV/DMIP
January 29, 2016

From:	Stanley H. Stern, Ph.D., Health Physicist, DMIP
Through:	Ira Krefting, M.D., Associate Director for Safety, DMIP
Through:	Libero Marzella, M.D., Ph.D., Director, DMIP
To:	File, NDA 200655
Subject:	Concerns about Ioflupane I 123 Injection for Intravenous Use (*DaTscan™*, NDA 022454) in comparison to F 18-FPCIT (structurally equivalent to *DaTscan™*) and in comparison to Fluorodopa F 18 Injection for Intravenous Use (^{18}F-L-DOPA, NDA 200655)
Correspondent:	(b) (4)
NDA 200655:	*Fluorodopa F 18 Injection* **NDA holder**: The Feinstein Institute for Medical Research, North Shore-Long Island Jewish Health System
NDA 022454:	*Ioflupane I 123 Injection (DaTscan™)* **NDA holder**: GE Healthcare
Correspondence:	Cover memorandum dated November 28, 2014 *[sic]*; Other material in correspondence package with later date: Nov 20, 2015
CDR receipt date:	November 24, 2015
Health physics:	Review initially requested Dec 10, 2015; formal assignment Jan 14, 2016

Request for health-physics review of correspondence

In a December 10, 2015, e-mail, Dr. Krefting asked (b) (4)

(b) (4)

Background

- *DaTscan™* (NDA 022454): initial approval January 14, 2011; supplement (revised labeling) approval: September 11, 2015.
- *DaTscan™ Injection indications and usage:* "DaTscan (Ioflupane I 123 Injection) is a radiopharmaceutical indicated for striatal dopamine transporter visualization using single

Reference ID: 3879489

photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations."

- *Fluorodopa F 18 Injection* (NDA 200655): complete response October 22, 2013; re-submission December 15, 2015; review pending; internal meeting January 20, 2016.
- *Fluorodopa F 18 Injection indications and usage:* "Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes (PS)."
- *General correspondence package, subject of this health physics report* — comprised of three categories of material:

(b) (4)

  - Documents and excerpts related to 6-fluoro-(18F)-L-DOPA (^{18}F-DOPA) [3].

Subject of correspondence, summary

In consideration of the relatively longer duration and larger radiation absorbed dose for ^{123}I-Ioflupane *(DaTscan™)* in the striata [4] compared to the duration and dose for ^{18}F-FPCIT residency in the basal ganglia [2], and also in regard to the poorer resolution, lower sensitivity, and longer procedure time of SPECT-^{123}I-based imaging versus PET-^{18}F-based imaging,

(b) (4)

Reviewer conclusion and recommendation

Conclusion:	For the reasons delineated in the following reviewer analysis and discussion, (b) (4).
Recommendation:	No regulatory action is indicated.

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/s/

STANLEY H STERN
01/29/2016

IRA P KREFTING
02/01/2016

LIBERO L MARZELLA
02/01/2016

November 6, 2013

Division of Medical Imaging Products

Clinical Review Memorandum

NDA: 200655
Investigational agent: Fluorodopa F 18 injection
Sponsor investigator: Feinstein Institute
Reviewer: Louis Marzella

Summary
In a letter dated October 25, 2013 the applicant request a face to face meeting with FDA to clarify the deficiencies in the FDA's October 22, 2013 complete response letter to the NDA. The applicant states that the proposed agenda of the meeting is to provide responses to the CR letter to clarify misunderstandings and confusions in their previous responses to FDA. The applicant's list of specific clinical questions does not contain actual questions, data or verifiable information. There are no concrete proposals to provide new clinical evidence of effectiveness. The claims, anecdotes, and explanations are not substantive enough to be the basis of a meaningful discussion.

Assessment and Plan
From a clinical perspective the meeting is denied because it does not contain meaningful questions or proposals for discussion. The new information the applicant provides should be included in an eventual NDA resubmission.

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/s/

LIBERO L MARZELLA
11/06/2013

MEMORANDUM DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
CDER/OND/ODE-IV

Date: 10/15/2013
From: Shaw T. Chen, M.D., Ph.D., Deputy Director, Office of Drug Evaluation-IV
To: File, NDA-200655
Subject: Complete Response for NDA 200655, FDOPA (F-18 Fluorodopa)

This is the ODE memo to concur with the decision to issue a Complete Response (CR) for this NDA, as recommended by the Division of Medical Imaging Products (DMIP). FDOPA is a Positron Emission Tomography (PET) imaging agent to visualize dopaminergic (b) (4) in the striatum of adult patients with suspected Parkinson's Disease (PD) or Parkinsonian Syndromes (PS).

This submission is deficient in many critical elements and overall does not support the approval of this NDA. Of the review disciplines, only pharmacology-toxicology and clinical pharmacology recommend approval, other reviewers, including CMC, clinical/statistical and inspections of both manufacturing facilities and clinical data, all have described serious deficiencies that could not be resolved at the end of this review cycle. The Division has reached a conclusion to issue a CR and provided a list of issues for the applicant to resolve and move forward. This position is concurred by the Office.

The long and complicated regulatory history of this drug's development has been described in detail by Dr. Ye in her medical review and summarized in the CDTL's memo by Dr. Gorovets and in the Division Director's memo by Dr. Marzella. Some PET agents, including FDOPA, have been used clinically for many years under the expanded access program of their active INDs and are allowed to charge patients to recover costs. This NDA submission represents an attempt to remediate this temporary measure and to obtain a formal marketing status for the drug. However, after an earlier submission was refused to file by the Division on 3/19/2010 (see medical reviews for reasons), the applicant's efforts have not produced an approvable package with this resubmission.

Major regulatory and scientific issues of this NDA are summarized as follows, a complete list of all CR deficiencies will be provided in more detail in the action letter.

I. Efficacy and Safety of FDOPA

As pointed out by the medical reviewers, there is no Integrated Summary of Efficacy (ISE) in this 505(b)(2) application which relies in part on published literature for evidence of safety and efficacy of FDOPA in the proposed indication. An extensive literature review by FDA in conjunction with the public discussion at the Advisory Committee (AC) on July 28, 2000 concluded that, despite substantial clinical experience and numerous publications, the efficacy of FDOPA had never been demonstrated convincingly in adequately designed studies. More recent publications that were not available for the past AC meeting are presented in the current

Reference ID: 3390034

submission (of the 8 identified in the application as supportive for efficacy, 7 were published after 2000). Of the publications, the review team consider two are of better designs and potentially useful (Studies 016 and 021), but dismiss the other 6 reported studies as non-supportive - a conclusion concurred by this Office. In addition, this submission also presented the report of a study conducted by the sponsor (Study 015). These 3 studies are described in further details and commented in the medical reviews by Drs. Ye/Gorovets/Marzella. The main reasons that their results cannot be relied upon as evidence of efficacy are reiterated as follows.

Study 015, "Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research",
The fatal flaw of this study is the use of clinical diagnosis (including the response to treatment for PD), instead of anatomical or histopathological findings, as the standard of truth. As imaging data are usually employed to confirm clinical diagnosis, the latter cannot be used to validate the former during development, even if the images were interpreted independently by three readers blinded to clinical information (as the applicant claims). In other words, as Dr. Ye also noted, if the clinical diagnosis is the truth, then there is no need for the imaging study. The integrity of the data is also questioned by the clinical reviewer and the GCP inspector as no documentation of such multiple readings has been submitted. As described in the medical reviews, the applicant has concluded that, using the clinical diagnosis as the standard of truth, the test performs with 100% sensitivity and 100% specificity, and the readers agreed with each other completely. Again, without an appropriate standard of truth, this cannot be a reasonable estimate of the performance characteristics of the imaging study.
Also noted by the medical review team, no protocol has been provided for this retrospective analysis. Thus no key elements of a prospectively designed protocol such as hypothesis testing, analytical plan, definition of primary endpoint, are available for rigorous regulatory review.

Study 016, "Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging", Eckert et al, *Movement Disorders*, 22: 167-173, 2007
As commented by Dr. Gorovets, this clinical follow-up of a subset of 27 patients in Study 15, who did not respond to treatment and had a negative F-18 FDOPA PET scan, could potentially serve as an estimate of specificity. The number of patients, however, is too small to provide adequate confidence in the estimate and another problem, again, is validation of the standard of truth. Absence of PD or PS requires well documented long term follow-up. Out of these 27, eight patients (the applicant increased to all 27 at the Late Cycle Meeting, but without follow-up submission of data in an amendment) were followed for a minimum of 2 years and were eventually diagnosed with a condition other than PS. Despite FDA's request for appropriate documentation of clinical follow up for this important patient cohort, no such data have been submitted to date.

Study 021, "Direct Comparison of FP-CIT SPECT and FDOPA PET in Patients with Parkinson's Disease and Healthy Controls", Eshuis, et al, *Eur J Nuc Med Mol Imaging* 36: 454-462, 2009
This is an exploratory study to compare sensitivity and specificity of DaTscan and F-18 FDOPA PET. This study enrolled patients in various stages of PD (11 early-, 17 advanced-stage and 20 age-matched controls), but lack subjects without a definitive diagnosis of PD yet (those who may benefit from the imaging study). The one-year follow-up clinical diagnosis was used as the

standard of truth. While the study did show that DaTscan SPECT and FDOPA PET were similar in their performance, the data are too limited to serve as evidence of their equivalence. The reviewers (e.g., see Dr. Ye's review) are also concerned about the definition of positive scans, which is based on an exploratory quantitative measurement, and how the specificity was calculated (age-match control as the standard of truth for negative?).

Overall, data from these three studies are not sufficient to provide substantial evidence of effectiveness.

Safety
While not much safety information was submitted in this application, lack of such data is not considered a CR issue. Based on the experience of its use under IND, reports in literature, non-clinical evaluation and other relevant data (e.g., clinical pharmacology, experience with Levodopa), the review team is not concerned about the safety of this drug. This conclusion is concurred.

II. Other Deficiencies

The deficiencies identified by other review disciplines, as summarized in the reviews by CDTL and the Division Director, are all serious enough to serve as the basis for issuing a CR to this application. See the CR letter for a complete listing, the major ones include:

Integrity of clinical data
Many violations of GCP standards (see inspection report by Dr. John Lee of OSI and summary of the issues by Dr. Gorovets) raise questions about the reliability of most of the information provided by the applicant.

CMC & GMP
Major remaining CMC issues are specifications for the precursor and drug product, data for stability at low pH and validation of the HPLC purity test. Approval by microbiology reviewers is also pending a "complete response to microbiology deficiencies", which include (b) (4) the lack of adequate validation for bacterial endotoxins assay at low pH.

Violations of GMP reflect in general the above deficiencies in CMC/microbiology. To this date, the applicant has not addressed satisfactorily the issues identified in the inspection report (see Form 483). The Office of Compliance (OC)'s current recommendation for this NDA is "Withhold".

III. Path Forward

For the product to be approvable in the next review cycle, the sponsor needs to follow the instruction in the CR letter and address all the deficiencies identified. Among those listed, a well-designed new clinical study with an acceptable truth standard is the most critical. The applicant should also comply with GCP regulations, provide better documentation of the trial.

IV. Availability under IND

While this submission cannot support marketing of FDOPA as an approved imaging agent, there is no new data suggesting that the product quality and clinical effects of FDOPA have changed significantly from the past IND experience. The Division's recommendation to keep the IND active, to continue expanded use and to allow charging patients for cost, is thus reasonable and concurred by the Office.

V. Conclusions

The benefit/risk assessment is straightforward for this product, as provided in the reviews by the clinical team and the Division Director's memo. Based on the data presented in this submission, FDOPA cannot be approved as a PET agent for the proposed indication of imaging in Parkinson's Disease or Parkinsonian Syndrome. A CR should be issued as recommended by the Division.

cc:
ORIG: NDA- 200655
Director, ODE-IV
Director, DMIP
Review Team, NDA-200655

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/s/

SHAW T CHEN
10/15/2013

Summary Review for Regulatory Action

Date	September 20, 2013
From	Libero Marzella MD, PhD
Subject	Division Director Summary Review
NDA **Supplement #**	200655 0
Applicant Name	Feinstein Institute for Medical Research
Date of Submission	October 22, 2012
PDUFA Goal Date	October 22, 2013
Proprietary Name **Established (USAN) Name**	None Fluorodopa F 18
Dosage Form **Strength**	Injection 0.42-8.33 mCi/ml
Proposed Indication	Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.
Recommended Action for NME:	Complete Response

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Brenda Q. Ye MD
Statistical Review	Satish Misra PhD
Pharmacology Toxicology Review	Sally Hargus PhD
CMC Review	Martin Haber PhD
Microbiology Review	Robert J. Mello PhD
Clinical Pharmacology Review	Christy S. John PhD
OSI	Jong H. Lee MD
CDTL Review	Alex Gorovets MD
OSE/DRISK	Amarylis Vega MD, MPH

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Reference ID: 3377297

1. Introduction

The Feinstein Institute for Medical Research has submitted this 505(b)(2) NDA application for Fluorodopa F 18 Injection, a radioactive diagnostic agent for use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adults with suspected Parkinsonian syndromes.

Regulatory history of fluorodopa F 18 in the US
Fluorodopa F 18 is a radiopharmaceutical for PET imaging. Historically fluorodopa F 18 was produced in the US in compliance with United States Pharmacopeia (USP) PET compounding standards and monographs and under licensure by the Nuclear Regulatory Commission (NRC). Fluorodopa F 18 was legally marketed for clinical use in positron emission tomography (PET) imaging of neurologic and oncologic conditions. The applicant (Feinstein Institute) has legally produced fluorodopa F 18 and used the drug in clinical practice at the NorthShore University Hospital Center for several years.

The more recent legislative history of fluorodopa F 18 and other PET drugs in clinical use begins with the determination by FDA that approved applications for PET drugs are required because these drugs are not deemed generally recognized as safe and effective under section 201(p)(1) and (p)(2) of the Federal Food, Drug, and Cosmetic (FDCA) Act.

The 1997 Food and Drug Administration Modernization Act (FDAMA, section 121) directed FDA to establish appropriate procedures for the approval of PET drugs and appropriate requirements for current good manufacturing practice (cGMP) for such drugs. Before establishing the procedures and requirements the Act required FDA to consult with patient advocacy groups, professional associations, manufacturers, and physicians and scientists licensed to make or use PET drugs. FDA could begin to require the submission of New Drug Applications (NDAs) two years after the establishment of the procedures and requirements for the approval of PET drugs.

FDA conducted a review of the scientific literature for the most commonly used PET drugs including fluorodopa F 18 and held meetings of the Medical Imaging Drugs Advisory Committee (MIDAC) and other public meetings to discuss the findings of the reviews.

At a July 28, 2000 public meeting FDA and the Institute for Clinical PET held an “Informal Discussion of Literature Reviews of Safety and Efficacy Data for PET: 150-water and 18F-fluorodopa” The meeting concluded that available literature data for fluorodopa F 18 were insufficient to support efficacy in any patient population. It was decided that discussion of fluorodopa F 18 at MIDAC was not warranted at the time. The PET community anticipated the development of additional data from new studies and encouraged FDA to plan to reassess the evidence of fluorodopa F 18 efficacy. For the meeting transcript[1] and the literature listings[2] see the links below.

[1] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM182861.txt
[2] http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/Manufacturing/UCM183457.pdf

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In a March 10, 2000 notice in the Federal Register, FDA announced its findings that certain commonly used PET drugs, when produced under conditions specified in approved applications, can be found to be safe and effective for certain indications.[3] FDA also announced the approval procedures for these PET drugs and indications and invited manufacturers of these drugs to submit applications for approval.

FDA had approved NDAs for three PET drugs: sodium fluoride F 18 to define areas of altered osteogenic activity, rubidium chloride 82 for assessing regional myocardial perfusion in the diagnosis and localization of myocardial infarction and fludeoxyglucose (FDG) F 18 injection for the identification of regions of abnormal glucose metabolism associated with foci of epileptic seizures. FDA also announced its findings of safety and effectiveness for FDG F 18 for use in oncology and for assessment of myocardial hibernation, and for ammonia N 13 for evaluation of myocardial blood flow. FDA also issued a guidance document that describes how to complete either a 505(b)(2) or a 505(j) application for the PET products addressed in the Federal Register notice.

On December 9, 2009 FDA issued regulations establishing cGMP for PET drugs. The regulations in 21 CFR Part 212 apply to the production, quality control, holding, and distribution of new PET drugs. The publication of these procedures triggered the implementation timeline specified by the 1997 FDAMA. At the request of drug manufacturers, FDA extended the timeline until June 12, 2012. After that date any facility wishing to continue to produce PET drugs for clinical use was required to have submitted an NDA, an ANDA or to be producing the drugs under an IND. All PET producers must be operating under an approved NDA or ANDA, or effective IND, by December 12, 2015.

The clinical reviewer (Dr. Ye) and the cross discipline team leader (CDTL, Dr. Gorovets) provide a more detailed discussion of the difficult regulatory history of this application.

On October 30, 2009 the applicant submitted a marketing application for fluorodopa F 18. FDA refused to file the application because of inadequate clinical, nonclinical, and CMC data. Notably the NDA did not appear to contain data from adequate and well-controlled studies. FDA acknowledged that many patients had received fluorodopa F 18 injection at the applicant's clinical site. FDA encouraged the applicant to summarize the safety and diagnostic efficacy data from that experience.

The applicant has raised concerns about the ability of his institution to continue to make fluorodopa F 18 available for clinical use to patients with PS. The applicant has also criticized FDA for what they perceive is a lack of fairness in the action FDA took with fluorodopa F 18 (refusal to file) compared to the action FDA took with other PET drugs (e.g. fludeoxyglucose F18, ammonia N 13) for which FDA conducted a literature review and made a finding of safety and effectiveness.

[3] http://www.fda.gov/ohrms/dockets/98fr/031000a.txt

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FDA encouraged the applicant to submit an expanded access IND with a request to charge for fluorodopa F 18. FDA allowed the expanded access IND to proceed and granted the request to charge on June 21, 2012.

Regulatory history of fluorodopa F 18 in the EU

Fluorodopa F 18 was approved for marketing for clinical use in Europe through mutual recognition under the "well established clinical use" procedure. France served as the reference member state. According to Article 10A of Directive 2001/83/EC, this approval procedure applies if a medicinal product has been in well-established use within the European Community for at least 10 years, and has recognized efficacy and an acceptable level of safety. Under this procedure the results of pre-clinical tests or clinical trials are not needed for approval and can be replaced by appropriate scientific literature. The review team examined the assessment report for fluorodopa F 18 provided by the French Health Authorities (Dr. Y M Chevalme of ANSM) and determined that no new clinical trial data had been developed for this EU approval. In the EU, fluorodopa F 18 has a neurology indication similar to that of ioflupane I 123 (DaTscan, approved in the US and EU) and additionally has an oncology indication. Fluorodopa F 18 is marketed in the EU under the name Dopacis or IASOdopa.

Ioflupane I 123

Ioflupane I 123 (DaTscan) is a radiopharmaceutical for Single Photon Emission Computed Tomography (SPECT) imaging approved in the US in 2011 as an adjunct to other diagnostic evaluations in adults with Parkinsonian syndromes (PS) for differentiating essential tremor from tremor due to PS. Ioflupane I 123 targets the dopamine transporter and the resulting image is similar to the image produced by fluorodopa F 18.

Focus of summary review

The summary review focuses on the serious deficiencies in the clinical studies submitted by the applicant. These deficiencies include the lack of a well defined prospective clinical protocol, statistical analysis plan, procedure for blinded independent interpretation of the PET images, and lack of an adequate truth standard. In addition the FDA review of the literature did not identify adequate and well controlled clinical trials. The integrity of the data from the studies conducted by the applicant has also been questioned.

The proposed remedy is to conduct an adequate and well controlled trial in patient with early features of Parkinsonism with a final clinical diagnosis established by a consensus panel of movement disorder experts who evaluate data over an adequate period of follow up (e.g. 3 years).

2. Background

Fluorodopa F 18 is chemically similar to dopamine and like dopamine it is taken up by dopaminergic neurons. Parkinsonian syndromes are characterized by diminished striatal dopamine uptake principally due to loss of dopaminergic neurons. Fluorodopa F 18 uptake and retention can be visualized in a PET image and might be useful in the evaluation of patients suspected of having a Parkinsonian syndrome.

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3. CMC/Device

I concur with the conclusions reached by the chemistry reviewer Dr. Martin Haber regarding the manufacturing of the drug product and drug substance. Dr Haber determined that major chemistry manufacturing and control issues in the NDA include the specifications for the chiral precursor, drug product specifications, data for stability at low pH, and validation data for the HPLC purity test. I agree with Dr. Haber's recommendation for a complete response action.

I concur with the overall Office of Compliance recommendation to withhold approval because the manufacturing site inspection was not acceptable. The form 483 listed 10 observations related to current good manufacturing practices, standard operating procedures, and various product specification issues.

I concur with the recommendation by the product quality microbiology reviewer Dr. Robert Mello for a complete response action. Dr Mello determined that (b) (4) the bacterial endotoxin assay is not validated at the low pH of the dug product.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology and toxicology reviewer Dr. Sally Hargus that there are no outstanding pharmacology or toxicology issues that preclude approval of this application. Dr. Hargus deferred review of the labeling. The applicant did not submit any original nonclinical data and Dr Hargus determined that no original data were required.

The applicant submitted summaries of 20 publically available reports on the pharmacology and toxicology of fluorodopa F 18. In addition the applicant cited the review of the preclinical data conducted by FDA and the results of the review discussed at the 2000 Public Meeting with the Institute for Clinical PET. The FDA supervisory pharmacologist Dr. Adebayo Laniyonu performed that review. At that time, the available nonclinical information on fluorodopa F 18, and the nonclinical and clinical scientific literature on levodopa were judged to be sufficient to support the clinical use of fluorodopa F 18 for PET imaging studies.

Dr. Hargus concludes that at this time the available information is acceptable and conventional pharmacology and toxicology studies for fluorodopa F 18 are not needed because of: clinical experience with fluorodopa F 18, without safety signals; historical database and clinical experience with levodopa administered at daily doses approximately a thousand-fold greater than the one-time mass dose of fluorodopa F 18; similarity in the metabolism and disposition of levodopa and fluorodopa F 18; very low risk of toxicity based on the radioactive dose of fluorodopa F 18 of (b) (4) 5 mCi.

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5. Clinical Pharmacology/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology reviewer Dr. Christy John that there are no outstanding clinical pharmacology issues that preclude approval of this application. Dr. John deferred review of labeling. Dr. John's clinical pharmacology review is based on 14 scientific publications submitted by the applicant. No clinical pharmacology studies were conducted by the applicant and none were needed.

Dr. John found that the proposed mass dose (approximately (b)(4) mg) and the radioactive dose (approximately 5 mCi) was based on review of publications and are acceptable. Fluorodopa F 18 undergoes decarboxylation by aromatic amino acid decarboxylase; to decrease decarboxylation and increase bioavailability to the brain, patients are pretreated with carbidopa. Dr John found the selected carbidopa dose of 150 mg based on the publications to be acceptable. The applicant's clinical study required patients to discontinue any Parkinsonian medications at least 12 hours prior to the PET study to avoid the possibility of interaction with fluorodopa F 18 and this procedure was judged to be reasonable.

6. Clinical Microbiology

This section is not applicable. No clinical microbiology data were provided and none are needed.

7. Clinical/Statistical-Efficacy

I concur with the assessment of the clinical and statistical reviewers that the application does not contain any acceptable verifiable evidence of fluorodopa F 18 performance characteristics or evidence of the drug's clinical utility. I agree with the recommendation for a complete response action. The following is a summary of the key evidence and of the conclusions reached by Drs. Ye and Zalkikar for the two studies (study 15 and 16) conducted by the applicant.

Study 15
The principal efficacy study (study 15) is titled: "Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research". This retrospective single-center study enrolled 196 subjects. Of these 196 subjects, 11 were healthy volunteers and 185 were patients who were referred by a movement disorder specialist and exhibited at least two of the features of Parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). Subjects received 150 mg of carbidopa one hour before fluorodopa F 18 Injection (4-5 mCi).

The primary efficacy endpoint was the qualitative binary visual assessment of the fluorodopa F 18 PET scan. The scan was judged to be positive if the uptake of fluorodopa F 18 in the

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striatum was reduced as evidenced by a diminished size and shape of the putamen and caudate (crescent shaped structure) unilaterally or bilaterally. The PET scan was judged to be negative (i.e. consistent with no loss of dopaminergic neurons) if full crescent-shaped structures were visualized in the striatum. The applicant states that a total of 158 out of 185 patients were classified as positive by three independent readers blinded to the clinical diagnosis. The applicant concludes that the study outcome was no false positive and no false negative scans and complete agreement among the three independent readers.

The critical weakness of the study is that each patient's clinical diagnosis at the time of the PET scan was considered the standard of truth. For the 158 patients whose initial clinical diagnosis was "Parkinson's disease" and who were responding to treatment, a fluorodopa F 18 scan provides no additional clinically useful information. FDA therefore does not agree with the cited diagnostic performance measurements as 100% for sensitivity and 100% for specificity.

The study was not conducted according to a pre-specified protocol, and definitions of primary efficacy endpoint and standard of truth that would normally be specified by a protocol, are not well-defined for the study. The NDA contains no documentation that fluorodopa F 18 PET images were read independently by three readers or that the readings were performed without clinical information. The FDA inspectors determined that none of the audited cases contained documentation that the images were read by three blinded readers.

Study 16
This study is a continuation of the clinical study # 15 conducted by the applicant to further evaluate the patients that exhibited Parkinsonian symptoms but had a negative fluorodopa F 18 scan. The applicant states that the 27 patients with negative scans were followed for 2-4 years. Drs. Ye and Zalkikar determined that only 8 of the 27 patients were followed to obtain the patient's final clinical diagnosis. Clinical data from such a small number of patients and with so much missing data do not provide a reliable assessment of the performance characteristics of fluorodopa F 18.

8. Safety

I agree with the conclusions of the preclinical and clinical reviewers (Drs. Gorovets, Hargus, Laniyonu, and Ye) that fluorodopa F 18 does not pose important safety risks based on the single administration of a small mass dose and a small radioactive dose. The extrapolation to fluorodopa of the clinical safety experience with levodopa seems reasonable.

The applicant states that none of the subjects of the study experienced adverse events. No other clinical safety data were collected. The original FDA literature review of fluorodopa F 18 and the present update have not identified safety signals. The adequacy of safety assessments in published studies generally cannot be assessed and the data cannot be verified.

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9. Advisory Committee Meeting

No advisory committee meetings are planned.

10. Pediatrics

The applicant requested a full waiver of pediatric studies in an amendment to the NDA on January 3, 2013. Dr Ye and Dr. Gorovets agreed that studies of fluorodopa F 18 would be impossible or highly impractical in pediatric patients because Parkinsonian Syndromes are found mostly in adults. On June 5, 2013, the FDA Pediatric Review Committee agreed with granting a full pediatric waiver.

11. Other Relevant Regulatory Issues

There are important relevant regulatory issues related to OSI audits for compliance with good clinical practice (GCP) in the conduct of the applicant's studies. Form 483 was issued for failure to prepare and maintain adequate case histories, and inadequate investigational drug disposition records with respect to dates, quantity, and use by subjects. Specifically, Dr. Lee's report states that the subject files typically lacked documentation of the presence at enrollment of at least two features of PD and/or responsiveness to PD drugs. None of the case records examined contained evidence of PET scan interpretation by three separate blinded readers. For study 16 none of the subject files contained clinical follow-up confirmation of absence of PD symptoms and signs.

12. Labeling

No substantive labeling reviews were conducted because of multiple deficiencies with the application. While the resolution of PET images is superior to the resolution of SPECT images (b) (4)

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

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I concur with the recommendations for a complete response action made by the NDA reviewers in the following disciplines: chemistry manufacturing and controls, microbiological quality, clinical, and statistics. This application provides no acceptable measurements of the test scan's performance characteristics or evidence of the test scan's clinical utility.

I concur with the withhold approval recommendations by the manufacturing facility inspectors and note the serious deficiencies identified by the clinical site inspectors that call into question the integrity of the clinical study data.

- Risk Benefit Assessment

The important clinical and statistical deficiencies of the clinical studies conducted by the applicant preclude any conclusions about the efficacy of fluorodopa F 18. Review and inspectional findings of the clinical experience summarized by the applicant in the NDA shows that the data are not reliable.

The FDA review of the scientific literature in 2000 led to the conclusion that the publications at that time did not support the efficacy of fluorodopa F 18. In this NDA review cycle FDA has re-evaluated the more recent scientific literature and has examined reports prepared for marketing authorizations by other health authorities. However, FDA has not identified reports of adequate and well controlled studies of fluorodopa F 18 for the use proposed by the applicant. As such there in no substantial evidence of efficacy of the drug.

At the time of the NDA late-cycle meeting FDA provided to the applicant a complete listing of the deficiencies identified in the NDA. Subsequently FDA inspectors have identified serious GCP deficiencies. The CR letter will describe in some detail how to address the NDA deficiencies. However the applicant has stated that they lack the resources or personnel with the experience and qualifications to design and conduct an adequate and controlled clinical study of fluorodopa F 18. The applicant has been unable to obtain support form other government agencies, professional organizations, or commercial manufacturers for the clinical development of the drug.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

The DRISK reviewer Dr. Vega deferred a final discussion on any appropriate risk management strategy until after the applicant provides a satisfactory response to the anticipated complete response letter.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable

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/s/

LIBERO L MARZELLA
09/21/2013

Cross-Discipline Team Leader Review

Date	September 09, 2013
From	Alex Gorovets, MD
Subject	Cross-Discipline Team Leader Review
NDA#	200655
Applicant	Feinstein Institute for Medical Research
Date of Submission	10-22-2012
PDUFA Goal Date	10-22-2013
Proprietary Name / Established (USAN) names	Fluorodopa F-18 injection/F-18 Fluorodopa
Dosage forms / Strength	(b) (4) 5.0 mCi
Proposed Indication(s)	For use in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes
Recommended:	*Complete Response*

1. Introduction

The subject of this Cross Disciplinary Team Leader (CDTL) review is the New Drug Application (NDA) 200655 for F-18 Fluorodopa (FDOPA), a radiopharmaceutical proposed for use with Positron Emission Tomography (PET) in patients with parkinsonian syndromes.

The applicant is the Feinstein Institute for Medical Research where the drug is being produced. It is a 505(b)(2) application which relies in part on published literature for evidence of safety and efficacy of F-18 FDOPA in the proposed indication and also provides data from a single study conducted by the applicant. There is no approved marketing application in US for F-18 FDOPA.

The applicant proposes the following indication for F-18 FDOPA: *Fluorodopa F 18 Injection is a* (b) (4) *used in Positron Emission Tomography (PET) to visualize dopaminergic* (b) (4) *in the striatum in adult patients with suspected parkinsonian syndromes (PS).* (b) (4)

Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.

This review document addresses the evidence submitted by the applicant in support of the stated claim, considers the issues of clinical utility and product quality, and provides an assessment of risk and benefit of FDOPA-PET. The document refers to analyses and review

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findings from multiple disciplines. During the review process, no significant disagreements have been encountered among the reviewers.

2. Background

Rationale for Product Development
Fluorodopa is chemically closely related to dopamine. In the basal ganglia region of the brain, F-18 labeled fluorodopa (FDOPA) is converted to F-18 Fluorodopamine by aromatic amino acid decarboxylase (AAAD). Like dopamine, it is taken up by the dopaminergic neurons. The main component of the basal ganglia, striatum consisting of caudate nucleus and putamen, is the primary area of the brain affected by dopaminergic neuron loss in movement disorders like Parkinson's disease (PD) and other parkinsonian syndromes (PS). Such a neuronal loss is associated with a decline in an overall striatal dopamine uptake which is reflected by a diminished F-18 labeled fluorodopa uptake as would be visualized on a PET image.

PD is a well characterized progressive neuro-degenerative disorder of unknown etiology most noted for its tremor in addition to certain other motor abnormalities and neurologic signs. Diagnosis is established clinically and certain symptoms can be treated medically. Early diagnosis is sometimes problematic and PD not uncommonly, especially in general practice, has to be differentiated from Essential Tremor, a benign condition, which can also be treated medically but quite differently from PD.

A normal striatal complex has a characteristic comma-like appearance on a radionuclide uptake scan. In parkinsonian patients, the uptake is diminished and the typical appearance is lost.

Regulatory History
F-18 FDOPA has long been a research tool in studies of Parkinson's related, or parkinsonian, syndromes and movement disorders but its clinical usefulness has been long debated as well. The primary clinical reviewer of this application, Dr. Brenda Ye, in her summary of the regulatory history of FDOPA (see pages 8-9 of her review) cites the 2000 Public Meeting involving FDA where it was concluded "that available literature data for F-18 FDOPA were insufficient to support efficacy in any patient population". The rest of her summary documents the lengthy history of the regulatory relationship between the FDA and the current applicant.

F-18 FDOPA has been produced at Feinstein Institute and used in clinical practice at the NorthShore University Hospital Center for many years as an "unapproved" PET drug with a USP monograph. As explained in the recently published FDA Guidance on Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs, the Food and Drug Administration Modernization Act of 1997 (FDAMA, or "the Modernization Act") provided that "certain unapproved PET drugs would not be considered adulterated until the new current good manufacturing practice (CGMP) regulations for PET drugs (21 CFR part 212) took effect, if the production facility maintained compliance with United States Pharmacopeia (USP) monograph expectations for the specific drug".

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The Guidance cites twelve PET drugs which had USP monographs as of September 1, 2011. Fluorodopa F-18 injection is listed as one of these drugs.

The Guidance further states that "the publication of the final rule on CGMP for PET drugs on December 10, 2009 triggered the requirement that all producers of PET drugs submit applications by December 12, 2011" and that "all PET producers must be operating under an approved NDA or ANDA, or effective IND, by December 12, 2015."

The current applicant has an active IND (78861) since 2008 which has existed mostly in a "pre-IND stage" until 2012 when the enrolment of patients into an Expanded Access program under this IND has been approved by the FDA.

The applicant has first submitted the current NDA (200655) in 2009 but the FDA found the application to be seriously deficient and issued a "Refuse to File" letter. So this is now a re-submission following the refuse-to-file determination.

During this review cycle, multiple deficiencies and review issues have been identified by reviewers from various disciplines and communicated to the applicant before and after the Filing meeting, after the Midcycle meeting and at the Late Cycle Meeting. Of note, following the Filing meeting, the review team estimated that deficiencies remaining at the time were mostly review issues which would have to be further analyzed, and the application was filed.

Other Relevant Background
A Single Photon Emission Computed Tomography (SPECT) agent, I-123 Ioflupane, or DaTscan, has been recently approved in US and in Europe for dopamine transporter visualization in striatum. It targets a different neuronal protein, a dopamine transporter, but an overall imaging appearance is similar to FDOPA. In patients with PS, I-123 Ioflupane is indicated for use in differentiating essential tremor from tremor due to PS.

F-18 FDOPA has been approved in Europe for a neurology indication similar to DaTscan and an oncology indication and is distributed by a commercial manufacturer under the name DOPACIS.

3. CMC/Device

The following is excerpted from the primary Chemistry, Manufacturing and Controls (CMC) review by Dr. Martin Haber (a list of the required specifications is included to help assess the extent of ongoing deficiencies).

Fluorodopa F-18 Injection drug product is a sterile product for intravenous injection containing 5 – 100 mCi of fluorodopa F-18 in (b) (4) *mL of sterile water* [the proposed volume has been since modified]. *The drug product specifications follow the USP drug product monograph for fluorodopa F 18 injection and include tests for appearance, radionuclidic*

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identity, radiochemical identity and purity, chemical identity, radionuclidic purity, assay (amount of radioactivity), specific activity (mCi/mmol), pH, (b) (4), bacterial endotoxin testing, sterility testing, osmolality and chemical impurity testing for (b) (4) breakthrough. The expiry is limited by the short F-18 half-life and is set at 10 hours after synthesis.

The drug substance is 6-[18F]-fluoro-L-3, 4-dihydroxyphenylalanine or F-18 labeled FDOPA. Carrier added F-18 fluorine is produced in a cyclotron at the Feinstein Institute. (b) (4)

The recommended dose is (b) (4) 5 mCi. The sterile drug product (5-100 mCi at end of synthesis) is supplied in a capped (b) (4) multi-dose (b) (4) glass vial.

A number of CMC deficiencies have been identified throughout the current review cycle and various information requests have been sent to the applicant and specifically, among others, on 12/28/2012 and 05/31/2013. At the time of the completion of the primary review on 06/13/2013, the CMC reviewer was recommending a Complete Response because the sponsor had not responded adequately to those requests. In particular, the specifications for the drug product and drug substance precursor have not been finalized, data justifying a non-USP conforming pH have not been provided and validation data for the HPLC chiral identity and purity method have not been provided.

The Product Quality Microbiology reviewer, Dr. Robert Mello, has also identified a number of deficiencies which were being communicated to the applicant throughout the review cycle. These include the issues related to sterility testing, endotoxin testing, (b) (4) testing as well as the description of the whole set-up where the drug is produced to ensure that the drug production at this site, from a microbiology perspective, complies with the regulations that apply to a drug approved for marketing. At the time the primary review has been filed on 06/04/2013, the reviewer has concluded that "due to the deficiencies in sampling and validation of (b) (4)" the sterility and non-pyrogenicity of the drug product could not be fully assured.

Following the Good Manufacturing Practice (GMP) inspections in May 2013, the applicant was issued a Form 483 listing 10 observations. Overall, the inspectional observations paralleled the CMC and Microbiology review issues and deficiencies. So far, the applicant's responses have not satisfied all of the deficiencies, and currently, the Office of Compliance (OC) recommendation for this NDA is "Withhold".

The CMC and the Product Microbiology reviewers have just filed review updates based on applicant's submissions in August. Of note, the final drug product volume has now been revised by the applicant from (b) (4) mL to the range (b) (4) mL. The persistent review issue has been the pH of the drug product being measured as (b) (4) whereas the specified pH range in the Fluorodopa F-18 USP monograph is (b) (4) (e.g., higher). The new proposed specification range for the product pH is now (b) (4). Adequate supporting stability data at

different pH values have not been provided. Validation data for the HPLC purity test or a validation plan have still not been provided. At this time and for this review cycle, the CMC recommendation for this NDA is still Complete Response. Major remaining CMC issues are specifications for the chiral precursor, drug product specifications, data for stability at low pH and validation data for the HPLC purity test.

As for the Microbiology, the updated assessment states that the application is "approvable" pending a "complete response to microbiology deficiencies". Given that, most likely, no additional amendments, even if submitted, will be reviewed in this cycle, the recommended action, as clarified during the Wrap-up meeting on 08/28/2013, is a Complete Response. The remaining deficiencies are (b) (4) and the lack of adequate validation of the bacterial endotoxins assay to address the low pH (b) (4)) of the drug product.

It is important to note that at the Wrap-up meeting both disciplines, the CMC and the Product Microbiology, confirmed that, although at present the remaining deficiencies prevent an approval of this NDA based on the applicable NDA regulations, it would be safe to continue to use this drug from a product quality standpoint under the currently active IND application.

4. Nonclinical Pharmacology/Toxicology

The main aspect of pharmacologic and toxicologic evaluation of F-18 FDOPA is that F-18 FDOPA and Levodopa, a well established therapeutic drug for PD, are nearly identical molecules. Prescribed therapeutic doses of Levodopa for chronic daily use significantly exceed a one-time intravenously administered F-18 FDOPA mass dose of about (b) (4) mg or less as cited in this discipline review. The radioactive dose of (b) (4) 5.0 mCi is thought to present an acceptable risk in terms of radiation exposure.

Of further note is that, as described in the review by the primary Pharmacology/Toxicology reviewer, Dr. Sally Hargus, FDA has already conducted a review and evaluation of F-18 FDOPA Injection in preparation for a Public Meeting in July 2000. FDA has determined at the time that the available nonclinical pharmacology information on F-18 FDOPA, together with the Pharmacology/Toxicology information and clinical literature on Levodopa, can be considered adequate to support clinical use of Fluorodopa F 18 Injection for PET imaging studies.

No additional nonclinical data were required by FDA to be submitted with the current application. The Pharmacology/Toxicology review team recommends approval.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology reviewer, Dr. Christy John, confirms that the proposed dose of F-18 FDOPA is (b) (4) 5 mCi administered as an intravenous injection. The selection of dose was based on the applicant's review of literature. The primary information for clinical pharmacology review of this submission has been derived from fourteen publications submitted by the applicant. No clinical pharmacology studies were conducted by the applicant.

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The mass dose associated with the proposed radioactive dose is cited in this review as (b) (4) mg which is different from the (b) (4) mg dose cited in the Pharmacology/Toxicology review. The difference stems from a wide range of the product's Specific Activity (SA). Issues associated with the product's SA have been addressed in a greater detail in the CMC review. The product specification calls for a minimal SA of (b) (4) mCi per mmol. The mass dose, cited by the Clinical Pharmacology review, has been derived from this SA value. The actual product's SA can be significantly greater leading to a dose calculation cited in the Pharmacology/Toxicology review.

As part of its mechanism of action and as already described in the Background section above, F-18 FDOPA undergoes decarboxylation by the enzyme AAAD. In order to decrease decarboxylation by AAAD and increase FDOPA bioavailability to the brain, patients are pretreated with carbidopa, a known inhibitor of AAAD. According to Dr. John, the applicant has selected the carbidopa dose of 150 mg based on the assessment of peer-reviewed publications.

Following the intravenous administration, F-18 FDOPA is cleared from the blood with a biologic half-life of about 1 to 3 hours. The half-life of the F-18 radioisotope is known to be 110 minutes. Radiation dosimetry studies have identified urinary bladder as a critical organ and, although the exposure has been estimated to be well below doses that would cause concern, adequate hydration and post-administration voiding would be routinely recommended.

No drug interaction studies have been reported. However, as pointed out by Dr. John, it is not known whether drugs that are used to treat Parkinsonian syndromes can alter the disposition of FDOPA or the accumulation/retention of 18F in the striatum or the rest of the brain. For this reason, the reviewer agrees with the applicant's recommendation to discontinue any Parkinsonian medications at least 12 hours prior to the PET study. No special population studies or organ impairment studies have been reported. Based on the clinical experience with Levodopa, an effect of F-18 FDOPA on QT/QTc prolongation is not expected.

The Clinical Pharmacology review team recommends approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical- Efficacy

In assessing the efficacy data, the applicant as well as the primary clinical reviewer, Dr. Ye, and the primary statistical reviewer, Dr. Satish Misra, have emphasized the so called Study-15, a single center unpublished retrospective study conducted by the applicant. Altogether, in the

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current submission, the applicant attempts to rely on reports from nine studies, of which eight are publications. Of these eight, six publications as detailed by the primary reviewer do not appear to contribute to the evaluation of efficacy and will not be discussed further. The other two studies presented as possibly providing evidence of efficacy of F-18 FDOPA are Study-16 and Study-21. Study-16 is a published study of patients who actually represent a subset of patients from Study-15. Study-21 is a published study comparing F-18 FDOPA and DatScan, an approved imaging agent.

Study-15, titled "Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research", involved 185 patients who were referred by neurologists presumed to be movement disorder specialists, with all patients having had at least two out of four "cardinal" signs of PD (tremor, bradykinesia, rigidity, abnormal gait). Of these, 158 patients have responded to therapy and were designated as "PD" on enrollment. A clinical indication for referring these patients for imaging is unclear as they already had a clinical diagnosis consistent with PD and had responded to treatment. There were also 27 patients who have not responded to treatment and were designated as "non-PD". A reason for selecting any of the patients for this imaging study is unclear as no protocol has been provided. It is not clear how long the PD signs have been present in each patient prior to motor disorder specialist evaluation or prior to imaging.

Each patient received 4.5 – 5 mCi dose of F-18 FDOPA prior to undergoing PET imaging. The images were visually interpreted as positive or negative, with exploratory quantitative measurements being recorded as well. According to the applicant, all the F-18 FDOPA images were interpreted independently by three readers blinded to clinical information. An important issue questioning the integrity of the submitted data has been raised in this regard by the clinical reviewer and confirmed during the GCP inspections of the clinical site as no record has been presented documenting that each image has in fact been interpreted independently by each of the readers.

The results of Study-15 showed that all patients with "PD" had positive images, all patients with "non-PD" had negative images, and all readers agreed with each other. The applicant has concluded that the test performs with 100% sensitivity and 100% specificity. The clinical reviewer and the statistical reviewer both have found this interpretation to be unreasonable because the study was conducted without an acceptable standard of truth and no performance characteristics could be estimated from such a study. Not only the study does not appear to have been designed to demonstrate the clinical utility of FDOPA PET imaging in a population of patients who could benefit from such imaging, it also does not appear to have been designed to address the measurement of the test's reliability and performance. There was no pre-specified standard of truth, no known statistical analysis plan and no proposed hypothesis testing. The applicant states in the application that patients have been followed for three to four years after FDOPA imaging, indicating its accuracy, but no such data have been provided. So this appears to be an exploratory study showing data with 100% correlation between the imaging and the clinical diagnoses which require confirmation in a clinically relevant setting.

Study-16 is a published study (*Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging: Eckert et al Movement Disorders, Volume 22, No 2, pp 167-*

173, 2007) consisting of a clinical follow-up of a subset of patients from Study-15. These were the 27 patients who did not respond to treatment and had a negative F-18 FDOPA PET scan. Out of these 27, eight patients were studied with FDG scans, which were unrevealing, but they also ended up being followed for a minimum of 2 years by a movement disorder specialist to obtain patient's final clinical diagnosis. All eight were diagnosed with a condition other than a parkinsonian syndrome.

The results of Study-16 suggest a potential clinical utility for FDOPA PET in confirming an absence of PD in patients not responding to PD therapy. However, these are observational data in only eight patients. As noted by Dr. Ye, following the Post-Midcycle Communication teleconference, the applicant submitted an NDA amendment to further clarify that only eight out of 27 patients had a clinical follow up. Then at the Late Cycle Meeting, the applicant claimed that this was incorrect and that all 27 had a clinical follow up. FDA encouraged the applicant to submit the appropriate data addressing the clinical follow up in this important patient cohort but no such data have been submitted to date.

Study-21 is a publication (*Direct Comparison of FP-CIT SPECT and FDOPA PET in Patients with Parkinson's Disease and Healthy Controls: Eshuis, et al Eur J Nuc Med Mol Imaging 36: 454-462, 2009*) of an exploratory study which, as analyzed by Drs. Ye and Misra, aimed to compare sensitivity and specificity of DaTscan and F-18 FDOPA PET. The study evaluated 11 early-stage PD patients, 17 advanced-stage PD patients, and 20 age-matched controls. Each of the PD patients in the study underwent both SPECT and F-18 FDOPA PET. All patients were followed for 1 year after the scans, and the follow-up clinical diagnosis was used as the standard of truth. The study used exploratory quantitative imaging measurements to provide binary scan interpretations (positive or negative) and had a variety of other limitations as was pointed out by Dr. Ye. Taking into account its exploratory nature, the study did show that DaTscan SPECT and FDOPA PET were similar in their performance.

In conclusion, the submitted data are quite limited and not sufficient to provide substantial evidence of effectiveness. The clinical and statistical deficiencies have been well summarized in the Briefing package for the Late Cycle Meeting. Bothe clinical and statistical reviewers recommend a Complete Response.

8. Safety

There are essentially no safety data submitted in this NDA except for a record of all patients in Study-15 not having a single adverse event, as reviewed by Dr. Ye. The lack of data is balanced by the lack of safety signals from multiple exploratory studies involving F18 FDOPA. There is also a large safety database for Levodopa (see the related discussion above in the Pharmacology/Toxicology section).

9. Advisory Committee Meeting

No Advisory Committee meetings have been planned for this NDA in this review cycle.

10. Pediatrics

Pediatric waiver has been given as PD does not occur in children.

11. Other Relevant Regulatory Issues

As summarized by Dr. John Lee of OSI, the GCP inspections of the applicant's clinical site (Studies -15 and -16) have revealed that available records do not appear to meet the GCP standards for an NDA. A prospective study protocol and case report forms (CRFs) were not used and important study records (including source records) were not available for inspectional review. It is further noted that a Form 483 was issued for: (1) failure to prepare and maintain adequate case histories, and (2) inadequate investigational drug disposition records with respect to dates, quantity, and use by subjects.

Specifically, Dr. Lee's report states that the subject files typically lacked documentation of at least two cardinal features of PD and/or responsiveness to PD drugs and, for all subjects, the case records lacked evidence of PET scan interpretation by three separate blinded readers. Of further importance, for Study 16, none of the subject files contained documentation (clinical follow-up confirmation) of continued absence of classical PD symptoms and signs.

These findings question the reliability of most of the information provided by the applicant as one is left with having to rely on the applicant's testimony rather than data.

12. Labeling

In view of the significant data deficiencies no labeling discussions have taken place during this review cycle.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Cross Disciplinary Team Leader recommends a Complete Response (CR) to this application for the use of F18 FDOPA with the indication that states the following: "Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes (PS). (b) (4)
Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations."

- Risk Benefit Assessment

In assessing risks and benefits of this drug and the proposed imaging methodology it is clear that risk is minimal given the low level of radiation exposure, relatively small dose and an extensive related safety database.

However, the challenge here is demonstrating clinically relevant benefit. Having an imaging test to help with the differentiating parkinsonian syndromes from other movement disorders would be clearly useful. There is an approved imaging test already (DaTscan) helping differentiate essential and parkinsonian tremor. Having a PET agent serving a similar clinical purpose but with potentially better imaging resolution would still be useful but no data have been presented by the applicant or found in the literature addressing such an indication. Another possible clinical utility could be in early PD or in patients with early onset tremor but no data in such patients have been presented by the applicant. An area of clinical utility that the applicant did approach somewhat was the use of FDOPA PET in patients with an apparent clinical diagnosis consistent with PD but with no response to medical therapy directed at PD. The efficacy data presented from such patients have been however very limited and could not be relied on for approval.

The available data do show that FDOPA is biologically active and can in fact visualize the striatum but the data obtained at the applicant's clinical site and other presented clinical data do not provide information on the test's clinical utility or on the test's performance in a clinically relevant patient population. This particular application has been also affected by issues raising serious data integrity concerns. There are serious remaining drug specifications issues and quality concerns as well.

So while there is little risk indeed, no benefit has been demonstrated either. During the current review cycle the subject of European approval has been approached. Various European labels for FDOPA produced by a commercial European manufacturer were reviewed. The drug is approved, at least in UK, France and Spain, for PD and certain oncology imaging. The UK colleagues were contacted who reported that the drug had been approved based on earlier approval obtained in France. An English translation of the French review document justifying the approval was reviewed. The approval appears to have been based on "well established use". There was no indication that some data were available to the European regulators which were not available here. While the fact of European approval deserves further consideration, it bears no direct influence on the review of the current NDA at this time, given all the issues with product quality and clinical data deficiencies.

It should also be noted that a concern has been expressed that FDOPA imaging might in fact be not as efficacious as DaTscan imaging in early stages of PD, where it would be most useful, because of their different molecular targets. Whereas the dopamine transporters are known to undergo down regulation early in the course of the PD, the FDOPA target, AAAD, is thought to be subject to up-regulation. So early in the disease a decrease in the striatal uptake of an imaging agent might not be as apparent with an FDOPA type of an agent as with a DaTscan type. This, of course, can all be clarified only by clinical data.

At this time, in considering the marketing approval of FDOPA produced by the current applicant, this reviewer concludes that the lack of risk does not justify the lack of demonstrated benefit.

- Recommendation for Postmarketing Risk Management Activities

No risk management activities are planned.

- Recommendation for other Postmarketing Study Commitments

There are no postmarketing commitments.

- Recommended Comments to Applicant

The comments to the applicant are being finalized and will communicate three main recommendations: address all observations in both 483 Forms (GCP and GMP), resolve all product deficiencies, and conduct a clinical study in a patient population of intended use with a pre-specified standard of truth.

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/s/

ALEXANDER GOROVETS
09/10/2013

CLINICAL REVIEW

Application Type	NME NDA Resubmission After Refuse to File 505(b)(2)
Application Number(s)	200655
Priority or Standard	Standard
Submit Date(s)	10/22/2012, 12/17/2012, 1/3/2013, 4/5/2013
Received Date(s)	10/22/2012, 12/17/2012, 1/3/2013, 4/5/2013
PDUFA Goal Date	10/22/2013
Reviewer Name(s)	Brenda Ye, M.D.
Review Completion Date	June 20, 2013
Established Name	F-18 Fluorodopa
(Proposed) Trade Name	Fluorodopa F-18 Injection
Therapeutic Class	PET Diagnostic Radiopharmaceutical
Applicant	Feinstein Institute for Medical Research
Formulation(s)	Intravenous Injection
Dosing Regimen	(b) (4) 5 mCi
Indication(s)	To be used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the

	striatum in adult patients with suspected parkinsonian syndromes
Intended Population(s)	Adult patients with suspected Parkinsonian syndromes

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends Complete Response on the application because of the lack of robust efficacy data in the submission.

The reviewer recommends that the applicant continue enrolling patients in the clinical study conducted under the Expanded Access IND for F-18 FDOPA. The goal would be to obtain robust efficacy data through the study to supplement supportive clinical data available from literature.

The reviewer further recommends that during the upcoming Late Cycle meeting with applicant, in addition to discussing deficiencies identified by the FDA review team, a portion of the meeting be devoted to discussing updates on patient enrollment and patient follow-up plans for the clinical study conducted under the Expanded Access IND for F-18 FDOPA by the applicant.

1.2 Risk Benefit Assessment

Given the relatively small mass dose and one time administration of the proposed dosing for F-18 FDOPA, the reviewer does not consider the product posing additional safety concerns.

The product's proposed indication can largely be fulfilled by another product on the market: DaTscan. Hence there is no unmet medical need that could potentially be addressed by the product.

Lack of robust efficacy data is the main reason the application does not have a favorable benefit risk assessment.

2 Introduction and Regulatory Background

2.1 Product Information

Fluorodopa F-18 injection (F-18 FDOPA) is a PET radiopharmaceutical with a proposed indication for visualizing dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes. In the basal ganglia, F-18 FDOPA is converted to F-18 Fluorodopamine (FDA) by aromatic amino acid decarboxylase (AAAD). Thereafter, it is taken up into the storage vesicle where it can be released like dopamine by dopaminergic neurons. Figure 1 shows representative F-18 FDOPA PET images through basal ganglia, which are comma-shaped in the transaxial PET image slice. The comma-shaped basal ganglia include the

caudate nucleus ('comma head') and putamen ('comma tail'). On the left is an F-18 FDOPA PET image from a normal subject, showing uptake (denoted by red color) throughout the basal ganglia bilaterally. On the right is an F-18 FDOPA PET image from a Parkinson Disease (PD) patient, showing decreased uptake in putamen bilaterally while still retaining F-18 FDOPA uptake in the caudate ('comma head').

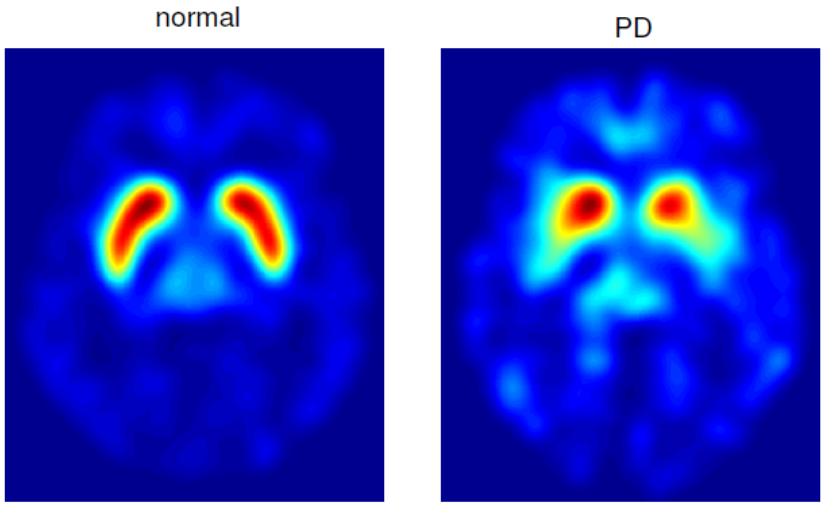


Figure 1: Images of F-18 FDOPA PET

2.2 Currently Available Treatments for Proposed Indications

Although no other drug has been approved for the proposed indication of "visualizing dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes" verbatim, DaTscan (I-123 FP-CIT, i.e. N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[123I]iodophenyl)nortropane) is approved for a similar indication:

> DaTscan is indicated for striatal dopamine transporter visualization by SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to Parkinsonian Syndrome (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy)

Figure 2 compares F-18 FDOPA PET images (panels a and b) with I-123 FP-CIT (DaTscan) SPECT images (panels c and d), in both healthy controls and patients with Parkinson Disease (PD). All four panels are axial images through basal ganglia (comma-shaped). In healthy controls (panels a and c), there are symmetric uptake/activity throughout the comma-shaped basal ganglia bilaterally. In early-stage PD (panels b and d), there is decreased uptake/activity in the left putamen, while the left caudate and right basal ganglia retain uptake/activity. The I-123 FP-CIT (DaTscan) SPECT images appear grainer than the F-18 FDOPA PET images because of technical differences between SPECT imaging and PET imaging.

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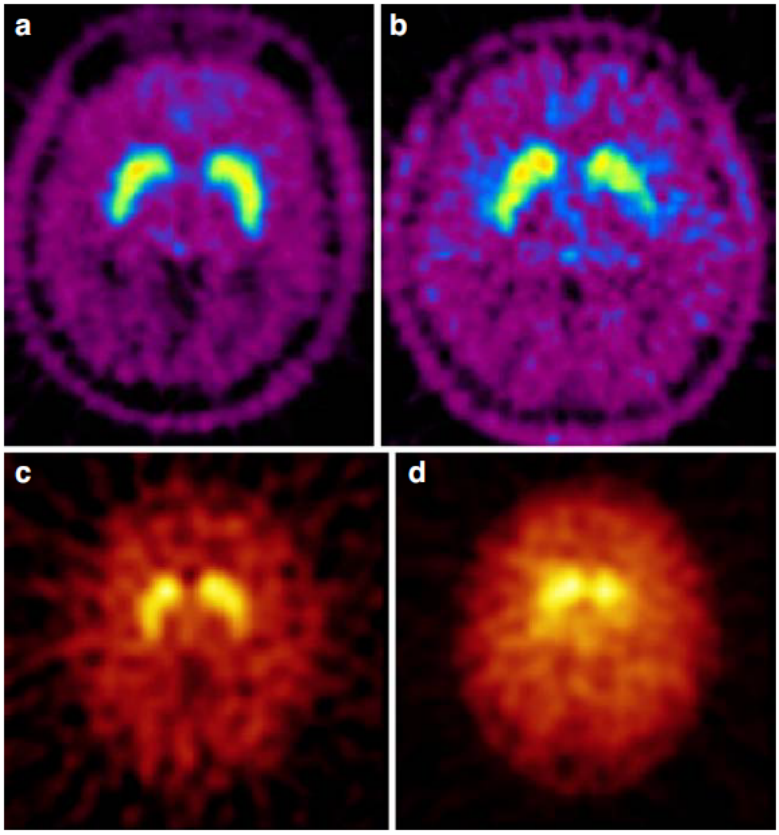


Figure 2: F-DOPA PET scans in (a) healthy controls and (b) patients with early-stage PD, and FP-CIT SPECT scans in (c) healthy controls and (d) patients with early-stage PD

2.3 Important Safety Issues With Consideration to Related Drugs

None

2.4 Summary of Presubmission Regulatory Activity Related to Submission

F-18 FDOPA was reviewed and discussed during the July 2000 Public Meeting between FDA and the Clinical PET community. The meeting concluded that available literature data for F-18 FDOPA were insufficient to support efficacy in any patient population.

The applicant, Feinstein Institute for Medical Research, approached the FDA in 2008 with additional literature publication. FDA expressed concerns that the selected literature publications were mostly exploratory in nature and lacked confirmatory clinical data on the efficacy of F-18 FDOPA for the proposed indication.

The applicant later submitted an NDA on 10/29/2009. User fee waiver was granted on 1/21/2010. The Agency refused to file the application on 3/19/2010 due to multiple filing

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deficiencies in clinical, pharmacology/toxicology, and clinical pharmacology sections (see DARRTS for Refuse-to-File Letter).

The applicant subsequently applied for an Expanded Access IND with Request to Charge on the product, and the Expanded Access IND was allowed to proceed and the Request to Charge granted on 6/21/2012.

Detailed time-line of F-18 FDOPA clinical considerations and the major submissions and responses to the NDA and PRE-IND archives are listed below:

a. July 28, 2000 Public Meeting for an "Informal Discussion of Literature Reviews of Safety and Efficacy Data for PET 150-water and 18F-fluorodopa," available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm182855.htm. In this meeting, Dr. Ramesh Raman of the FDA presented the results of his review of the literature. He noted that, of 472 researched articles, 21 articles were identified as potentially useful to estimating fluorodopa F18 efficacy, based upon prespecified criteria (e.g., designation of a truth standard). Dr. Raman noted that his review of these articles led him to conclude, "FDOPA marks the dopaminergic system and may be used as a biomarker. However, there was no single study that validated the other findings [need for clinical utility] that I talked about earlier." Dr. Raman emphasized that many studies compared patients with Parkinson's Disease to healthy volunteers/normal subjects. This observation is especially important since healthy volunteers/normal subjects do not typically undergo imaging tests and comparisons of imaging results between healthy volunteers and patients do not represent a clinically useful assessment of an imaging test's diagnostic performance.

b. April 28, 2008, during a PRE-IND telephone conference between FDA and the Sponsor, the main topic was a discussion of a proposed NDA to support the following claims for FDOPA:



Published literature formed the basis for the clinical studies section of the proposed label. In this discussion, the overall development plan for FDOPA was discussed. The Sponsor

explained [redacted] (b) (4)

c. October 8, 2008, the Sponsor provides a new submission to the PRE-IND archive, "Fluorodopa F18 Injection: A literature review of peer reviewed articles in support of its use as a positron emission tomography imaging agent." In the submission, the Sponsor noted that this literature review was provided in response to FDA requests discussed in the April 28, 2008 meeting.

d. November 28, 2008, the FDA communicated the results of its review of the October 8, 2008 submission in the form of an electronic communication (archived). FDA notes that, "The submission contains a selected overview of the literature (21 publications) in support of the proposed use. The studies cited are not adequate in design. Most of the studies assessed disease progression or response to various treatments [redacted] (b) (4) ." Subsequent comments provided detailed assessment of the two publications that reported studies of the largest sample size; FDA explained how well-designed "collective evidence" analyses of previously conducted studies (with verifiable data integrity) may provide the substantial evidence to support drug approval. The communication also provided advice on how to obtain the collective evidence.

e. April 2, 2009, communication from the Sponsor requesting advice on when to submit the NDA.

f. April 21, 2009, FDA relayed an electronic communication (archived) to the Sponsor explaining that an NDA may be submitted at any time.

g. April 27, 2009, FDA relayed an electronic communication (archived) to the Sponsor encouraging the conduct of a PRE-NDA meeting.

h. July 1, 2009, Sponsor submits a PRE-NDA meeting request background document. The document states that the desired indication is for, "[redacted] (b) (4) " The submission contained summaries of additional publications.

i. August 10, 2009, PRE-NDA meeting between FDA and the Sponsor. The Sponsor notes that he had revised the planned indication statement, as follows, "[redacted] (b) (4)

(b) (4)
." In response to FDA recommendation for at least one prospective clinical study that assessed use of the study drug, the sponsor explained that he did not have the resources available to conduct clinical studies and he also referred to an inability to obtain medical/investigator support from his institution. The FDA asked about the potential for other governmental agencies (e.g., NIH), institutions (e.g., Feinstein Transfer Office), professional scientific organizations (e.g., SNM, Parkinsonian Society) or pharmaceutical companies to assist with the drug's development; the sponsor explained that he has asked for assistance from all the suggested sources and has been unsuccessful in obtaining help to develop the drug. The Sponsor requested FDA to assist with the approval of the study drug as the FDA had done in the past for his other drugs, FDG and ammonia N-13. The FDA noted that an upcoming Peripheral and Central Nervous System Advisory Committee (August 11, 2009) may be beneficial to him.

j. August 25, 2009, request from the Sponsor for a meeting to discuss a newly revised indication for FDOPA. The Sponsor indicated that, following attendance at the advisory committee, he has decided to change the proposed drug indication to: "(b) (4)
"

k. August 31, 2009, FDA provides a letter that denied the proposed meeting, stating, "The proposed topic and questions pertain to items we expect sponsors to develop and vet within their organizations. Following submission of the NDA, we will review the appropriateness of the proposals, in light of the submitted data. We noted that we have already had one PRE-NDA meeting with you on August 10, 2009. At the present time, resources do not allow us the feasibility of a meeting to address the topic and questions you have proposed. Hence, we are denying the meeting. We encourage you to obtain the resources within your own organization to fully vet your proposals, to solidify the data and to prepare for a thorough NDA submission. We appreciate your efforts in preparation of the NDA. We encourage you to continue trying to obtain medical and regulatory expertise within your organization to help facilitate the development of your NDA."

l. October 30, 2009, FDA receives an NDA 200655 for the use FDOPA for the following indication, "(b) (4)
." The clinical studies section of the labeling (b) (4)

[redacted] (b) (4)

m. March 19, 2010, FDA issued a Refusal to File letter regarding NDA 200655, citing deficiencies that precluded ability to review the NDA within the following areas: administrative sections required by 21 CFR 314.50, clinical (lack of an integrated summary of efficacy; lack of supporting evidence for the proposed dose, lack of an integrated summary of safety, etc), pharmacology/toxicology (lack of the information required by 21 CFR 314.50(d)(2)—FDA recommended the sponsor refer to the July 28, 2000 meeting to resolve the deficiency), clinical pharmacology (lack of a human pharmacokinetic and bioavailability section). Within the letter, FDA stated, "Although not specifically a basis for our refusal to file your application, we have the following comments:

- The cited clinical efficacy data appears tenuous in its ability to support your proposed labeling. The application contains summaries of multiple publications as the confirmatory data for the clinical efficacy claims. However, this information does not appear to represent data from adequate and well-controlled studies. Only one study (published in two articles) appears to represent a multicenter, confirmatory trial. However this trial (Alan Whone et al, Ann Neuro, 2003) does not appear to be designed for evaluation the efficacy of fluorodopa F18 injection in PET imaging. Instead, the study appears to have been designed for evaluating the response of patients to treatment with ropinirole or levodopa. Therefore, the efficacy endpoint of this study does not match the proposed labeling indication for fluorodopa F-18 injection. Other study reports appear even more deficient in study design or relevance to the proposed claim of efficacy.

- We understand that many patients have been exposed to fluorodopa F-18 injection at your clinical site. When redeveloping your application, we encourage you to summarize the safety and nominal diagnostic efficacy data from this experience."

n. July 19, 2010 meeting between FDA and the Sponsor. The Sponsor explained the nature of clinical data at his clinical site. He stated that 185 Parkinsonian syndrome patients have been scanned with fluorodopa and 158 patient scans were found to be "positive" and 27 patient scans were found to be negative; he reported 100% sensitivity and 100% specificity. FDA pointed out that the test drug cannot be used as both a truth standard and a test. FDA also encouraged the Sponsor to re-examine his mathematics since the sensitivity calculation should be calculated as 85% and not 100%, based upon traditional methods for calculating sensitivity (scan reported as "positive" among 158/185 patients with disease). FDA further noted that specificity could not be calculated since all patients apparently had disease. FDA stated that the Sponsor's summary of his site's clinical data (in meeting background document) did not appear sufficient to support the

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safety and efficacy of the drug. When asked whether or not the Sponsor could resubmit the NDA, FDA confirmed that the Sponsor could submit an NDA.

o. September 27, 2010, the Sponsor sends a letter to FDA requesting "FDA to provide us with a letter indicating that the medical institutions will be able to use fluorodopa F18 PET imaging beyond the CGMP deadline (December 2011) with payment under a special IND. The letter further stated, "In the public meeting with FDA on July 28, 2000, the FDA representative indicated to us (in the minutes) that the 21 articles that he reviewed had potentially very valuable efficacy data and very strong statistical methods for imaging. He also indicated that in those studies the objectives were very clearly stated. The weakness, however, was that all the patients in the studies had no diseases. When we presented the more recent clinical study from our institute with patients having parkinsonian syndromes (with disease), FDA asked us to do the studies of patients without diseases. This is the exact reversal of the previous suggestion 10 years back. In the public meeting organized by FDA on July 28, 2000, FDA was satisfied with the efficacy and statistical methods of imaging for the studies reviewed. At that time, FDA did not express many concerns regarding the safety of this drug." The letter also requested, "Based on the information that was provided to FDA, I would like to request FDA to allow the submission of a NDA for this drug. I also would like to request FDA to consider filing our NDA for a priority review process if and when the NDA is submitted."

p. November 9, 2011, the Sponsor sends a letter to FDA stating, "Fluorodopa F18 PET study cancellations is going to affect patient management from December 2011 onwards unless FDA allows the use of this drug beyond December 2011.

q. December 2, 2011, FDA conducts telephone meeting with the Sponsor. FDA explained the IND submission process to the Sponsor.

r. December 2011, FDA issues "Notice of FDA Exercise of Enforcement Discretion for PET Drugs." The notice states, "If a facility wishes to continue to use PET drugs for clinical use after June 12, 2012, they must have submitted a New Drug Application (NDA) or an Abbreviated New Drug Application (ANDA) by that date, or be producing the drugs under an Investigational New Drug application (IND)."

s. December 12, 2011, Sponsor sends FDA a letter stating, "I am working hard to submit an NDA for the PET drug fluorodopa F18 injection before the June 12, 2012 deadline. Furthermore, "Any help from the FDA is greatly appreciated. The clinical trials are very expensive, involves millions of dollars and the medical centers cannot afford it. In the public meeting conducted by FDA on July 28, 2000, FDA reviewers presented the published clinical data and there were some discussion to support the clinical data with Additional information that was supplied by us to FDA. We were very close to an agreement regarding the submission of an NDA at that time. If fluorodopa F18 injection is going to be treated with the same standard as regular drug manufactured by pharmaceutical companies, we may not be able to satisfy FDA as in the case of FDG and ammonia. If FDA can treat fluorodopa F18 injection as an innovative PET drug which may disappear from the market, if not protected as described in the FDAMA Act, then we

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can find a common ground to approve this drug." The letter continues, "Our NDA 200655 did not get a fair review from the FDA clinical reviewers. We put 20 years of hard work by many centers to prepare this NDA. The NDA was not even filed by FDA. This was the last PET drug from the old order needs FDA approval. It was heartbreaking when we received the notice that the drug will not be filed. Unlike the other three PET drugs we created the NDA on our own without FDA help. Instead of helping us the reviewers raised the approval bar to the highest possible level."

t. January 19, 2012, the Sponsor sends a letter to FDA stating, "We would like to submit an NDA for fluorodopa F18 injection prior to June 12, 2012 to continue clinical use of this innovative PET drug to help Parkinsonian patients." The Sponsor again asks for FDA to approve the drug.

u. January 30, 2012, FDA sends an electronic communication (archived) to the Sponsor stating, "We acknowledge your correspondence of January 19, 2012, in which you summarize your plans to submit a NDA for fluorodopa F18 injection. You cite new information that you propose as importantly supporting the safety and efficacy of your drug." In light of new information, the FDA recommended the Sponsor conduct another PRE-NDA meeting.

v. April 16, 2012, PRE-NDA meeting between FDA and the Sponsor. In this meeting FDA encouraged the Sponsor to submit an expanded access IND with a clinical protocol. FDA clarified that the Sponsor may also submit a Request to Charge with the Expanded Access IND and that this Request to Charge is different from CMS/reimbursement considerations. FDA tried to explain that the IND process does not involve CMS. FDA detailed regulatory pathways. The Sponsor explained how FDOPA should be approved; FDA tried to explain how comparisons of fluorodopa performance between healthy subjects and patients with Parkinson's Disease did not represent a sufficient spectrum of disease for evaluation of fluorodopa performance. The Sponsor noted that they will work to submit an Expanded Access IND and also resubmit an NDA.

w. May 2, 2012, the Sponsor sends a letter to FDA requesting "exemption form the IRB approval and consent form for the submission of an Expanded Access IND with payment for fluorodopa F 18 injection."

x. May 16, 2012, FDA Advice Letter to the Sponsor stated that "we cannot exempt your proposed IND from the safeguards of the IND process, including the need for obtaining patient consent and obtaining authorization from your institutional review board. Administration of FDOPA to patients for clinical use under an IND necessitates compliance with the safeguards of the IND process, including the regulations governing informed consent (21 CFR 50) and institutional review boards (21 CFR 56)."

y. May 22, 2012, the Sponsor submitted an Expanded Access IND along with a Request to Charge for F-18 FDOPA.

z. June 21, 2012, the Request to Charge was granted, and the Expanded Access IND was allowed to proceed after potential hold issues were resolved.

2.5 Other Relevant Background Information

Fluorodopa F18 Injection is licensed as Dopacis and IASOdopa in several European countries including the United Kingdom, France, and Spain. Approved indications include uses in neurology and oncology. The neurology indication for Dopacis (F-18 FDOPA) is as follows according to the product's U.K. labeling:

> *PET with fluorodopa (^{18}F) is indicated for detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain parkinsonian syndromes. It can be used to differentiate essential tremor from parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system (Parkinson disease (PD), multisystem atrophy and progressive supranuclear palsy).*
>
> *PET with fluorodopa (^{18}F), on its own, is unable to discriminate between different parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system. It is also unable to discriminate between PD with and without tremor.*

The above neurology indication for Dopacis (F-18 FDOPA) is similar to the labeling indication for DaTscan (I-123 FP-CIT), in the sense that both products are indicated for differentiating essential tremor from tremor due to Parkinsonian Syndromes:

> *DaTscan is a radiopharmaceutical indicated for striatal dopamine transporter visualization by SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to Parkinsonian Syndrome (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy)*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The reviewer finds the submission quality of the application poor and raises concerns over the credibility of the clinical study conducted by the applicant.

Initial re-submission of the NDA on 10/22/2012 contains no study protocol, or case report tabulations (patient level data), or statistical analysis plan, or sample case report form used by PET image readers for the 'pivotal' study (designated as "*Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication*" in the application) conducted by the applicant onsite at the Feinstein Institute. The FDA review team regarded these missing information as potential filing deficiencies and requested such information in its 12/4/2012 Information Request to the applicant.

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The applicant submitted patient level data ("Fluorodopa Patient Data FDA"), sample case report form used to collect patient data ("Patient Data Collections Sheet"), study protocol, and Statistical Analysis in an amendment to the NDA on 12/17/2012.

The "Protocol"

The submitted "Protocol" is entitled "Measurement of Regional Glucose, Cerebral Blood Flow, and Dopamine Metabolism in Movement Disorders Using Positron Emission Tomography". The protocol does not have subject enrollment criteria, F-18 FDOPA PET reading methodology, standard of truth, data analysis plan, or safety monitoring plan. The Objectives of the Protocol were "*to measure regional cerebral dopamine concentration and cerebral blood flow and glucose metabolism in patients with brain movement disorders in order to determine the specific abnormalities of brain metabolism underlying the various clinical manifestations of these diseases*". The protocol's objectives are different from the study summaries presented in Module 2 and Module 5 of the NDA. Specifically, Module 2 Section 2.7.6 Synopses of Individual Studies list the objectives of Study #15 to be "Safety and efficacy of Fluorodopa F-18 Injection for differential diagnosis of Parkinsonian Syndromes" as duplicated below:

STUDY #15: The Study Conducted by The Feinstein Institute for Medical Research

Number of Study Centers	Design and Control	Drug Dosage and Route	Study Objective	Number of Patients Included/ Completed	Duration	Gender M/F	Diagnosis	Primary Endpoint
One	Blinded Study	4-5 mCi dose administered Intravenously	Safety and efficacy of Fluorodopa F 18 Injection for differential diagnosis of Parkinsonian Syndromes.	185/185	One day study	107/78	Parkinsonian Syndromes	Detection of loss or no loss of dopaminergic neurons. The results match with the end point.

Furthermore, F-18 FDOPA and carbidopa dosing are different between the study "Protocol" and the study summaries in Module 2 and Module 5 of the NDA – the "Protocol" uses 5-9 mCi F-18 FDOPA and 75 mg carbidopa given orally 30 minutes prior to FDOPA injection (or 25 mg carbidopa three times a day for 3 days prior to FDOPA injection), but Module 2 and Module 5 summaries of the study use 4-5 mCi F-18 FDOPA and 150 mg carbidopa given once orally. Given that study objectives and study drug dosing are different between the "Protocol" and study summaries in Module 2 and Module 5 of the NDA, it is obvious that the submitted "Protocol" and "Study #15: Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research" are two different studies. The fact that the applicant would submit a "Protocol" belonging to another study raises questions whether the "Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research" was conducted under a protocol at all. This raises concerns over the overall credibility of the clinical study conducted by the applicant.

Lack of Documentation of F-18 FDOPA PET Read by Three Readers

Despite the FDA review team's request to submit "an example of the forms used by the image readers to document their interpretation", the applicant did not submit this. The application contains the following summary table entitled "Percent Agreement on Sensitivity and Specificity Between [F-18 FDOPA] PET Scan Readers":

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	Sensitivity	Specificity
Reader I	100%	100%
Reader II	100%	100%
Reader III	100%	100%

However the application (including the 12/17/2012 amendment to the NDA on the FDA requested patient level data and case report tabulations) does not contain any additional information on the F-18 FDOPA PET read by the 3 readers. The submitted case report tabulation ("Fluorodopa Patient Data FDA") does not contain documentation that F-18 FDOPA PET images were read by 3 readers. The sample case report form ("Patient Data Collection Sheet") documents information on patient's clinical information, F-18 FDOPA injection dose, F-18 FDOPA PET image acquisition parameters, and the date of the F-18 FDOPA PET, but does not document F-18 FDOPA PET read results. It is unclear to the reviewer whether all 196 subjects' F-18 FDOPA PET images were read by the same 3 readers or only some of the PET images were read by 3 readers. The application does not contain information on basic information such as names of the three readers, credentials of the three readers, date(s) of the PET read (same as the F-18 FDOPA PET scan date?), and whether the readers were blinded to patient's clinical information. Without these essential information, the claim made by the applicant as summarized in the above table cannot be validated. The applicant's failure to submit "an example of the forms used by the image readers to document their interpretation" and the failure to submit documentations of PET read by three readers despite FDA review team's request again raise concerns on the overall credibility of the clinical study conducted by the applicant.

Response to FDA Inquiry on the Establishment of Standard of Truth
The clinical study conducted by the applicant appears to use patient's initial clinical diagnosis as the standard of truth based on Module 2 and Module 5 summaries. However the study "Protocol" submitted as an amendment to the NDA on 12/17/2012 does not provide details/definitions of the standard of truth. The patient level data ("Fluorodopa Patient Data FDA") submitted as an amendment on 12/17/2012 appear to designate some patients as having "PD", and other patients as "Suspected non-PD". During the Post-Midcycle Communication teleconference with the applicant on 3/25/2013, the FDA asked the applicant to provide more details on how each patient's clinical diagnosis (used Standard of Truth) was established. The applicant replied that "*A clinical study coordinator at the Feinstein Institute held telephone conversations with referring physicians and designated each referred patient as "Parkinson Disease" or "Suspected Non-Parkinson" based on the telephone conversation. No additional records of the telephone conversation were kept. The coordinator was the only one at the Feinstein Institute who had knowledge of the clinical status/diagnosis of each referred patient, and the coordinator retired in 2006. All patients included in the F-18 FDOPA NDA were from 2006 or earlier [italics are excerpt from Post-midcycle Communication Teleconference Minutes in DARRTS]*. The applicant essentially clears its responsibility of providing source data documenting how the standard of truth was established in the clinical study conducted by the applicant because the only person who had detailed knowledge of this inquiry retired from the Institute. This further raises concerns over the overall credibility of the clinical study conducted by the applicant.

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3.2 Compliance with Good Clinical Practices

Upon initial filing review of the NDA, the clinical reviewer noted that there was no statement of Good Clinical Practice on the clinical study conducted by the applicant. In order for the application to be filed, each pivotal study needs a statement of Good Clinical Practice, stating that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures. These filing deficiencies were conveyed to the applicant on December 4, 2012.

On December 17, 2012, the applicant submitted an amendment to the NDA. The cover letter of the amendment stated that the clinical study at the Feinstein Institute of Medial Research was conducted under the approval of the IRB and followed Good Clinical Practice. There were informed consent forms for all patients who participated in the study.

3.3 Financial Disclosures

The applicant states that they are only the manufacturer of this drug and have no connection or contact with any of the medical practitioners prescribing this imaging agent, and there are no financial interests between these medical practitioners and the applicant (Feinstein Institute for Medical Research).

There are no clinical trials sponsored by the applicant, although the applicant conducted one clinical trial onsite (Study #15). The investigators on this trial, Dr. David Eidelbert, M.D. (Head for Neurosciences at Feinstein Institute for Medical Research) and Dr. Thomas Chaly, Ph.D (Chief of Cyclotron/Radiochemistry at the Feinstein Institute for Medical Research) both signed and submitted FDA form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and reported no financial interests and arrangements.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

CMC reviewer recommends Complete Response. The recommendation on Complete Response is based on unresolved CMC deficiencies (applicant's response to FDA CMC Information Request has been inadequate) and pending overall cGMP recommendation by the Office of Compliance.

4.2 Clinical Microbiology

Clinical Microbiology reviewer recommends Complete Response. Review issues on product sterility have not been resolved.

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4.3 Compliance

The product is manufactured onsite by the applicant at the Feinstein Institute for Medical Research. This facility was inspected by the FDA district office during the NDA review cycle. The FDA district office recommends withhold on the facility.

4.4 Clinical Pharmacology

No review issues from Clinical Pharmacology. The Clinical Pharmacology reviewer finds the proposed dosing regimen for F-18 FDOPA, including the dosing regimen for carbidopa pretreatment, acceptable.

4.5 Office of Scientific Investigation

The Office of Scientific Investigation inspection report is pending at the time of completion of this review.

5 Sources of Clinical Data

Upon initial filing review of the application, the clinical reviewer noted the lack of patient level clinical data (case report tabulations) from the 'pivotal' study conducted by the applicant (designated as "*Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication*" in the application), among other filing deficiencies:

> *1) Both pivotal studies were conducted by the applicant onsite at the Feinstein Institute, yet the applicant has not submitted datasets for the pivotal studies. This is a major filing deficiency. This deficiency was not listed as a filing deficiency in the Agency's Refuse-to-File Letter, because neither study was included in the original NDA submission.*
> *The reviewer requests the Feinstein Institute to submit patient level data for at least Pivotal Study #1 (STUDY #15: Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research). Patient level data need to include at least the following information for each study subject: patient ID, date of FDOPA PET scan, results of FDOPA PET scan, date patient's truth standard (true diagnosis) was established, patient's truth standard and how it was established (e.g. clinical diagnosis), adverse events (yes, no, not available)*
>
> *2) The resubmission still lacks Integrated Summary for Efficacy (ISE) and Integrated Summary for Safety (ISS). Both were listed as filing deficiencies in the Agency's Refuse-to-File Letter. Since Module 2 Summaries now includes Overview of Efficacy, Overview of Safety, Summary of Clinical Efficacy, and Summary of Clinical Safety. One solution to salvage the repeated deficiencies in the ISE and ISS would be to ask the applicant to designate the clinical overviews and clinical summaries to 'double-up' as ISE and ISS. Since the lack of ISE and ISS were listed as filing deficiencies in the Agency's Refuse-to-File*

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Letter, the reviewer recommends the sponsor submit a written statement/designation as an amendment to the NDA.

3) Each pivotal study needs a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures

On December 4, 2012, the FDA review team communicated the filing deficiencies to the applicant:

Regarding NDA 200655: Fluorodopa F-18 Injection, we are currently conducting filing review of your NDA submission dated October 22, 2012, which we consider has much improved over the original NDA submission, 10/29/09. Nonetheless, we have identified the following potentially salvageable filing deficiencies:

The submission contains two study reports of "Controlled Clinical Studies Pertinent to the Claimed Indication":

- *"STUDY #15: Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research"*
- *"STUDY #16: Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging".*

In particular, "STUDY #15: Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research" appears pivotal to our review of the drug's safety and efficacy. This study was conducted by the applicant onsite at the Feinstein Institute for Medical Research, yet the applicant has not submitted case report tabulations (patient level data) for the study. This is a major filing deficiency. This deficiency was not listed as a filing deficiency in the Agency's previous Refuse-to-File Letter, because the study was not included in the original NDA submission.

The FDA review team requests the Feinstein Institute for Medical Research to submit patient level data (case report tabulations) for "STUDY #15: Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research". Patient level data need to include at least the following information for each study subject:

- *Patient ID*
- *Patient's clinical diagnosis upon referral to the Feinstein Institute. If the patient was suspected of Parkinsonism, indicate the date of the initial evaluation and the date at follow up when the eventual diagnosis of Parkinsonism (e.g. Parkinson's disease, multiple system atrophy, progressive supranuclear palsy) was made. For patients with an established diagnosis of Parkinsonism at the time of the initial referral, please identify the clinical severity of the disease and whether the patient had been on medications for PD.*

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- *Qualification of the physician who performed the evaluation of each patient (e.g. movement disorder specialist, neurologist, internist etc.)*
- *Date the first and last study patients were enrolled in the study. Listing of patients referred to the Institute for scanning during this time period who were not included in the study and reasons.*
- *Date of Fluorodopa F-18 PET scan*
- *Results of the Fluorodopa F-18 PET scan (can be binary read as you have proposed)*
- *Severity of loss of dopaminergic activity in the patients who had positive scans*
- *Patient's adverse events, if any. At a minimum, indicate yes, no, or not available for each patient*

2. The resubmission still lacks Integrated Summary for Efficacy (ISE) and Integrated Summary for Safety (ISS). Both were listed as filing deficiencies in the Agency's previous Refuse-to-File Letter. Since Module 2 Summaries now includes Overview of Efficacy, Overview of Safety, Summary of Clinical Efficacy, and Summary of Clinical Safety, you may submit a statement designating the clinical overviews and clinical summaries to 'double-up' as ISE and ISS. Alternatively, you may submit a written statement explaining why ISE and ISS are not needed for the NDA.

3. Regarding the study conducted by the applicant (STUDY #15: Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research) supply a statement of Good Clinical Practice, indicating that the study was conducted in compliance with institutional review board regulations (or was not subject to the regulations), and that it was conducted in compliance with the informed consent regulations. Also supply: 1) a copy of the protocol, including the statistical analytical plan, 2) an example of the case report forms used to collect patient data and 3) an example of the forms used by the image readers to document their interpretations. Additional information may be necessary as our review progresses.

On 12/17/2012, the applicant submitted patient level data, patient consent form, patient data collection sheet (sample case report form), study protocol, statistical analysis, and a cover letter as an amendment to the NDA. The patient level data (case report tabulations) were submitted as an Excel spreadsheet entitled "NSLIJ Health System Patient Data Set (1995-2004)". The spreadsheet includes columns for Date of Study, Protocol, patient names, Age, Sex, Clinical Diagnosis, Radiopharmaceutical, Dose (mCi), PET Scan Results, Adverse Events, and Referring Physician for each of the 196 subjects of the study. Subject enrollment (date of the F-18 FDOPA PET) of the study ranged from 1995 to 2004.

Besides the 'pivotal' clinical study conducted by the applicant (STUDY #15: Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research), the application also contains eight literature publications on clinical studies of F-18 FDOPA (Studies #16-23). Studies #1-14 of the NDA are literature publications on the biopharmaceutics, pharmacokinetics, and pharmacodynamics of F-18 FDOPA and have been reviewed by the FDA Clinical Pharmacology review team.

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5.1 Tables of Studies/Clinical Trials

5.3.5 REPORTS OF EFFICACY AND SAFETY STUDIES			
5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication			
Study #15	The Feinstein Institute	Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research	
Study #16	Eckert, et. al.	Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging	*Movement Disord* 2007;22:167-173
5.3.5.2 Study Reports of Uncontrolled Clinical Studies			
Study #17	Ito, et. al.	Striatal and Extrastriatal Dysfunction in Parkinson's Disease with Dementia: A 6-[^{18}F]Fluoro-L-Dopa PET Study	*Brain* 2002;125:1358-1365
Study #18	Rakshi, et. al.	A Comparison of the Progression of Early Parkinson's Disease in Patients Started on Ropinirole or L-Dopa: An ^{18}F-Dopa PET Study	*J Neural Transm* 2002;109:1433-1443
5.3.5.3 Reports of Analyses of Data From More Than One Study			
Study #19	Whone, et. al.	Slower Progression of Parkinson's Disease with Ropinirole versus Levodopa: The REAL-PET Study	*Ann Neurol* 2003;54:93-101
Study #20	Whone, et. al.	A Technique for Standardized Central Analysis of 6-Fluoro-L-Dopa PET from Multicenter Study	*J Nucl Med* 2004;45:1135-1145
5.3.5.4 Other Study Reports			
Study #21	Eshuis, et. al.	Direct Comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls	*Eur J Nucl Med Mol Imaging* 2009;36:454-462
Study #22	Jokinen, et. al.	Simple Ratio Analysis of ^{18}F-Fluorodopa Uptake in Striatal Subregions Separates Patients with Early Parkinson Disease from Healthy Controls	*J Nucl Med* 2009;50:893-899
Study #23	Brown, et. al.	Fluorine-18-Fluoro-L-DOPA Dosimetry with Carbidopa Pretreatment	*J Nucl Med* 1998;39:1884-1891

5.2 Discussion of Individual Studies/Clinical Trials

1) There are two "Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication":

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Study #15	The Feinstein Institute	Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research	
Study #16	Eckert, et. al.	Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging	*Movement Disord* 2007;22:167-173

Study #15 is a 'pivotal' study conducted by the applicant onsite at the Feinstein Institute for Medical Research. Study #16 (Eckert, et al.) is a literature publication of clinical follow-up results of a subset of patients in Study #15. These two studies will be further discussed in the next section of the review.

2) There are two "Study Reports of Uncontrolled Clinical Studies":

Study #17	Ito, et. al.	Striatal and Extrastriatal Dysfunction in Parkinson's Disease with Dementia: A 6-[^{18}F]Fluoro-L-Dopa PET Study	*Brain* 2002;125:1358-1365
Study #18	Rakshi, et. al.	A Comparison of the Progression of Early Parkinson's Disease in Patients Started on Ropinirole or L-Dopa: An ^{18}F-Dopa PET Study	*J Neural Transm* 2002;109:1433-1443

Study #17 is a publication of an exploratory study analyzing FDOPA influx constant (Ki) in various brain regions. All subjects were patients with Parkinson Disease, with one set of patients having idiopathic Parkinson Disease with dementia, and the other set of patients having idiopathic Parkinson Disease without dementia. Analyzing FDOPA influx constant (Ki) in various brain regions does not provide relevant clinical data to demonstrate the efficacy of F-18 FDOPA as a diagnostic radiopharmaceutical.

Study #18 is a publication of an exploratory study on disease progression (all patients were diagnosed with Parkinson Disease) and treatment response (to Ropinirole vs. L-Dopa). The focus of the study was to evaluate patient treatment response rather than to demonstrate the diagnostic efficacy of F-18 FDOPA PET. The study does not provide relevant clinical data to demonstrate the efficacy of F-18 FDOPA as a *diagnostic* radiopharmaceutical.

Both studies are exploratory nature, and both studies are conducted in patients who have already been diagnosed with Parkinson Disease (PD). Patients whose diagnoses remain unclear could potentially benefit from another diagnostic test such as F-18 FDOPA PET, but patients who have already been diagnosed with Parkinson Disease would not benefit from another *diagnostic* test. Therefore neither study was conducted in the product's intended population. Neither study provides relevant clinical data to demonstrate the efficacy of F-18 FDOPA in the product's intended population for the proposed indication.

3) There are two "Reports of Analyses of Data From More Thank One Study:

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Study #19	Whone, et. al.	Slower Progression of Parkinson's Disease with Ropinirole versus Levodopa: The REAL-PET Study	*Ann Neurol* 2003;54:93-101
Study #20	Whone, et. al.	A Technique for Standardized Central Analysis of 6-Fluoro-L-Dopa PET from Multicenter Study	*J Nucl Med* 2004;45:1135-1145

Study #19 is a publication of a clinical study designed to compare treatment response to ropinirole vs. L-dopa. All patients recruited were already diagnosed with PD. Study #20 is a publication of the technical portion of Study #19. The clinical study was conducted in patients who were already diagnosed with PD (rather than in patients whose diagnoses remain unclear and could potentially benefit from another diagnostic test such as F-18 FDOPA PET), and the focus of the study was to evaluate patient treatment response rather than to demonstrate the diagnostic efficacy of F-18 FDOPA PET. The study does not provide relevant clinical data to demonstrate the efficacy of F-18 FDOPA for the proposed indication.

4) There are three "Other Study Reports":

Study #21	Eshuis, et. al.	Direct Comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls	*Eur J Nucl Med Mol Imaging* 2009;36:454-462
Study #22	Jokinen, et. al.	Simple Ratio Analysis of ^{18}F-Fluorodopa Uptake in Striatal Subregions Separates Patients with Early Parkinson Disease from Healthy Controls	*J Nucl Med* 2009;50:893-899
Study #23	Brown, et. al.	Fluorine-18-Fluoro-L-DOPA Dosimetry with Carbidopa Pretreatment	*J Nucl Med* 1998;39:1884-1891

Study #21 is a publication of an exploratory study comparing sensitivity and specificity of I-123 FP-CIT SPECT (DaTscan) and F-18 FDOPA PET. This publication provides relevant clinical data on the efficacy (sensitivity and specificity) of F-18 FDOPA as a diagnostic radiopharmaceutical. The reviewer regards the study as one of the 'pivotal' clinical studies of the NDA (the other 'pivotal' clinical study being Study #15, the clinical study conducted by the applicant). This study will be discussed further in the next section of the review.

Study #22 is a publication of an exploratory study assessing whether a simple ratio analysis (SOR) of FDOPA uptake in various brain regions would reliably separate PD patients from healthy controls. The exploratory analysis on the simple ratio does not provide relevant clinical data to demonstrate the efficacy of F-18 FDOPA as a diagnostic radiopharmaceutical.

Study #23 is a publication of an exploratory study showing the effect of carbidopa pretreatment on FDOPA biodistribution and dosimetry. Review issues on carbidopa pretreatment dosing have been discussed by the FDA Clinical Pharmacology review team. The publication does not

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provide relevant clinical data to demonstrate the efficacy of F-18 FDOPA as a diagnostic radiopharmaceutical.

6 Review of Efficacy

Efficacy Summary

Study #15-23 in the NDA are designated as "Reports of Efficacy and Safety Studies". As discussed above the reviewer considers the clinical study conducted by the applicant (Study #15 and Study #16) and a publication comparing the sensitivity and specificity of F-18 FDOPA with DaTscan (Study #21) relevant in providing clinical data for the evaluation of the efficacy of F-18 FDOPA as a diagnostic radiopharmaceutical.

1) The clinical study conducted by the applicant (Study #15) has serious deficiencies:
   - The study is a retrospective single center study
   - The study was apparently 'conducted' without a pre-specified protocol, and hence key parameters of the study (e.g. definitions of primary efficacy endpoint and standard of truth) that would normally be specified by a protocol, are not well-defined for the study
   - The applicant apparently used each patient's clinical diagnosis at the time when the patient was referred to the Feinstein Institute for F-18 FDOPA PET as the Standard of Truth. Therefore "Possible PD", "Possible non-PD", and "Suspected non-PD" were regarded as standard of truth, but in fact these are clinical *suspicions* rather than *truth standard!*
   - Because of the wrong assumption to regard pre-imaging clinical suspicions (Possible PD vs. Possible non-PD, and "PD" vs. "Suspected-non-PD") as the standard of truth, the applicant's conclusions on the performance characteristics (100% sensitivity/specificity/positive predictive value/negative predictive value) are not valid.
   - The application does not contain any documentation that each F-18 FDOPA PET was read by three readers (the applicant fails to submit such documentation for PET image interpretations from 3 readers despite FDA's request). The applicant's claim that each of the 3 readers had 100% sensitivity and 100% specificity can not be regarded as valid without the applicant supplying source documentation for PET image read by 3 readers
   - The applicant used patient's pre-imaging clinical diagnosis as the standard of truth and apparently demonstrated that F-18 FDOPA PET results were 100% identical to each patient's pre-imaging clinical diagnosis. Another regulatory problem then arises – if F-18 FDOPA PET simply duplicates each patient's pre-imaging clinical diagnosis, it appears that F-18 FDOPA PET provides no additional clinically useful information. This would particularly be true for the patients whose pre-imaging clinical diagnosis was already "PD" – what clinically useful information does F-18 FDOPA PET add? One of the important regulatory considerations in evaluating the efficacy of a diagnostic radiopharmaceutical is an assessment of the drug's ability to provide clinically useful information.

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2) Study #16 is a publication of follow-up results of F-18 FDOPA PET negative patients in Study #15. It also has major limitations:

- The number of patients followed was small: eight patients out of 27 F-18 FDOPA PET negative patients from Study #15 were followed to obtain patient's final clinical diagnosis. So even though these 8 patients have final clinical diagnosis (all had "non-PD") as the standard of truth, eight patients is a small number
- The vast majority of patients in Study #15 apparently would not receive useful clinical information from another diagnostic imaging test such as F-18 FDOPA PET, as these patients already had a clinical diagnosis based on patient's symptoms and they were responding to antiparkinson medication, therefore F-18 FDOPA PET would not be indicated in these patients. For the small portion of patients who could potentially benefit from such an imaging test, only a small number of patients (8) had established standard of truth. Clinical data from such a small number of patients may not allow for the assessment of the accuracy/performance characteristics of the imaging test F-18 FDOPA PET.

3) Most of the eight literature publications (Study #16-23) do not provide relevant clinical data for the assessment of the efficacy of F-18 FDOPA as a diagnostic radiopharmaceutical, except one publication by Eshuis et al (Study #21).

4) Although Study #21 is relevant in providing clinical data for demonstrating the efficacy of F-18 FDOPA as a diagnostic radiopharmaceutical, the study has a number of major limitations:

- The study is a small single center study
- The study is exploratory rather than confirmatory in design
- All study patients were already diagnosed with PD, therefore patient population of the study is not a patient population that would clinically benefit from another diagnostic imaging test such as DaTscan or F-18 FDOPA PET
- Patients who potentially could benefit from another diagnostic imaging test such as F-18 FDOPA PET (e.g. patients with atypical signs, patients exhibiting symptoms of Parkinsonian syndromes but were not responding to antiparkinson medication) were excluded from the study
- The definition of positive scans (SOR below two standard deviations of mean SOR from healthy controls) is an exploratory quantitative measure and its threshold is arbitrarily set
- It is unclear how specificity was calculated which involves true negatives; it is unclear whether true negatives were simply healthy controls in the study, as all patients included in the analysis of the study had confirmed PD

5) The overall submission of the application is poor and the reviewer raises concerns over the overall credibility of the clinical study conducted by the applicant (see discussions under Submission Quality and Integrity in Section 3.1 of the review)

6.1 Indication

The applicant proposes the following indication for F-18 FDOPA:

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Fluorodopa F 18 Injection is a [redacted] (b) (4) *used in Positron Emission Tomography (PET) to visualize dopaminergic* [redacted] (b) (4) *in the striatum in adult patients with suspected parkinsonian syndromes (PS).* [redacted] (b) (4) *Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.*

6.1.1 Methods

As discussed above, the clinical review of efficacy focuses on two 'pivotal' studies in the submission – the clinical study conducted by the applicant (Study #15 and 16) and a literature publication comparing the sensitivity and specificity of F-18 FDOPA with DaTscan (Study #21).

6.1.2 Demographics

1) "STUDY #15: Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research"

The clinical study conducted by the applicant (Study #15) evaluated 196 subjects with F-18 FDOPA PET. Of these 196 subjects, 11 were normal controls (8 males, 3 females), and 185 were patients (107 males, 78 females) with at least two cardinal features of Parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorders).

The applicant conducted a statistical analysis comparing subject age across 3 subgroups: normal controls, FDOPA PET negative ("NEG-PD"), FDOPA PET positive ("POS-PD"). The analysis showed that there is significant age difference between the FDOPA PET positive group (56.75 ± 12.47 years) and the FDOPA negative group (45.30 ± 19.32 years). There was no significant age difference between the normal control group (58.64 ± 15.21 years) and the FDOPA positive group (56.75 ± 12.47). Summary demographics and analysis results on the age difference among the 3 subgroups are shown in Table 1.

Table 1: Summary of Subject Demographics (Study #15)

		Normal Controls N=11	FDOPA PET Negative ("NEG-PD") N=27	FDOPA PET Positive ("POS-PD") N=158	Overall Subjects N=196
Male	n (%)	8 (73%)	16 (59%)	91 (58%)	115 (59%)
Female	n (%)	3 (27%)	11 (41%)	67 (42%)	81 (41%)
Age	Mean ± SD (median; range)	58.64 ± 15.21 (68; 34-72)	45.30 ± 19.32 (42; 17-86)	56.75 ± 12.47 (54.5; 16-81)	54.76 ± 15.9

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Reviewer's comments: In the applicant's datasheet and analysis, FDOPA PET negative patients were designated as Negative for Parkinson Disease ("NEG-PD"); FDOPA PET positive patients were designated as Positive for Parkinson Disease ("POS-PD"). FDOPA PET negative ("NEG-PD") patients were significantly younger than FDOPA PET positive ("POS-PD") patients or normal controls. True Parkinson Disease is found generally in older people. Therefore the apparent high predictive value for F-18 FDOPA PET to predict PD vs. Non-PD is confounded by this significant age bias.

2) Study #21: Direct Comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls; Eshuis et al, *Eur J Nucl Med Mol Imaging*, 2009(36) 454-462 (Study #21)

Study #21 evaluated 11 early-stage Parkinson Disease (PD) patients, 17 advanced-stage PD patients, and 20 age-matched controls (Table 2). Each of the PD patients in the study underwent both I-123 FP-CIT SPECT and F-18 FDOPA PET. Each control had either I-123 FP-CIT SPECT or F-18 FDOPA PET (10 in each group). The 11 early-stage PD patients (51.3 ± 10.1 years) were younger than the 17 advanced-stage PD patients (64.5 ± 6.3 years). This age difference is expected, as Parkinson Disease is a progressive neurodegenerative disease, worsening as a patient's age advances.

Table 2: Summary of Subject Demographics (Study #21)

	Controls		Early-stage patients		Advanced-stage patients	
	FP-CIT	F-DOPA	FP-CIT	F-DOPA	FP-CIT	F-DOPA
No. of subjects	10	10	11	11	17	17
Men	5	5	8	8	15	15
Women	5	5	3	3	2	2
Age (years)						
Mean	60.2	61.4	51.3	51.3	64.5	64.5
SD	8.7	8.5	10.1	10.1	6.3	6.3

6.1.3 Analysis of Primary Endpoint(s) – Clinical Study of Fluorodopa F-18 Injection Conducted by the Feinstein Institute for Medical Research (Study #15)

Study #15 is a retrospective single center study conducted by the applicant onsite at the Feinstein Institute for Medical Research. The study evaluated 196 subjects with F-18 FDOPA PET. Eleven (11) of the 196 subjects were normal controls, and the other 185 subjects were patients referred to Feinstein Institute for F-18 FDOPA PET. According to the submission "all (185) patients were referred by a movement disorder physician and exhibited at least two of the cardinal features of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder)".

The NDA submitted on October 22, 2012 initially did not contain a study protocol. Upon FDA request, the applicant submitted a "Protocol" that apparently belongs to another study (see

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discussions under Submission Quality and Integrity in Section 3.1 of the review). The reviewer suspects that the study was not conducted under a pre-specified protocol, given the applicant's failure to submit the protocol upon FDA request. Because of the lack of a pre-specified protocol, many important parameters (e.g. definitions of primary efficacy endpoint and standard of truth) that normally would be specified by a protocol are not well defined for the study.

The study's primary efficacy endpoint apparently was the "detection of loss or no loss of dopaminergic neurons". Criteria for F-18 FDOPA PET Image Classification as Either Negative (no loss of dopaminergic neurons) or Positive (loss of dopaminergic neurons) are shown in Table 3.

Table 3: Criteria for F-18 FDOPA PET Image Classification as Either Negative or Positive

Image Classification Based on Visual Examination	Criteria for the Classification
Negative (normal)	Negative scans were characterized based on the uptake of Fluorodopa F 18 by the caudate and putamen bilaterally. Negative scans show a uniform uptake, as seen by the crescent shaped caudate and putamen.
Positive (abnormal)	A positive scan shows a reduced uptake of Fluorodopa F 18 by the putamen or putamen/caudate, either unilaterally or bilaterally, depending upon the severity of the disease.

It is unclear to the reviewer how each patient's standard of truth is established. The applicant apparently uses each patient's clinical diagnosis at the time when the patient was referred to the Feinstein Institute for F-18 FDOPA PET as the Standard of Truth. The following diagram from the application states that "Clinical Diagnosis as the Standard of Truth at the Time When the PET Scan was Requested".

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		Clinical Diagnosis as the Standard of Truth at the Time When the PET Scan was Requested		
		Possible PD	**Possible non-PD**	
		Positive	Negative	
Fluorodopa F 18 PET SCAN	Positive Loss of Dopaminergic Neurons	True Positive (TP) = 158	False Positive (FP) = 0	→ Positive Predictive Value = TP/(TP+FP) = 158/(158+0) = 1 = 100%
	Negative No loss of Dopaminergic Neurons	False Negative (FN) = 0	True Negative (TN) = 27	→ Negative Predictive Value = TN/(FN+ TN) = 27/(0+27) = 1 = 100%
		↓ Sensitivity = TP/(TP+FN) 158/(158+0)= 1 = 100%	↓ Specificity = TN/(FP+TN) 27/(0+27)= 1 = 100%	

Reviewer's comments: Note in the applicant's diagram above, Clinical Diagnosis at the time when PET scan was requested was listed as "Possible PD" and "Possible non-PD". However "Possible PD" and "Possible non-PD" are clinical suspicions rather than standard of truth!

The applicant regarded "Possible PD" and "Possible non-PD" as the standard of truth and counted 158 patients positive for "Possible PD" as true positives, and 27 patients negative for "Possible non-PD" as true negatives. However because the wrong assumption to regard pre-imaging clinical suspicion (Possible PD and Possible non-PD) as the standard of truth, the applicant's conclusions in the above diagram (100% sensitivity/specificity/positive predictive value/negative predictive value) are not valid.

The reviewer examined the patient level data (spreadsheet "Fluorodopa Patient Data FDA") submitted as an amendment to the NDA. The spreadsheet has a column for Clinical Diagnosis, and each subject's Clinical Diagnosis is listed as either "Normal" or "PD" or "Suspected non-PD". The spreadsheet also has a column for PET Scan Results, and each subject's PET Scan Results is listed as either "Normal" or "Positive". The spreadsheet does not list three PET reader's individual readings as commented in Section 3.1 Submission Quality and Integrity of the review. The study evaluated 196 subjects with F-18 FDOPA PET. There are 11 subjects whose PET Scan Results are Normal and Clinical Diagnosis is normal; 27 subjects whose PET Scan Results are "Normal" and Clinical Diagnosis is "Suspected non-PD', and 158 subjects whose PET Scan Results are "Positive" and Clinical Diagnosis is "PD" (Table 4)

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Table 4: FDOPA PET Results and Clinical Diagnosis in Study #15

FDOPA PET Results	Clinical Diagnosis			
	Normal	PD	Suspected non-PD	Total
Positive		158		158
Negative ("Normal")	11		27	38
Total	11	158	27	196

In response to FDA Information Request, the applicant submitted a sample case report form ("Patient Data Collection Sheet") that was used to collect patient data in 12/17/2012 amendment to the NDA. The "Patient Data Collection Sheet" has an entry for "Diagnosis", presumably patient's clinical diagnosis (or clinical suspicion) when being referred to Feinstein Institute for F-18 FDOPA PET. The applicant submitted one such sample form for a patient whose "Diagnosis" was "PD".

The reviewer has requested the FDA Office of Scientific Investigation (OSI) to inspect Feinstein Institute. In particular the reviewer has request the inspection to verify how and when "PD" vs. "Suspected non-PD" were determined, since this designation is being used as the standard of truth.

Furthermore, the reviewer has requested the FDA OSI inspection to verify that the 27 patients who had negative F-18 FDOPA PET indeed had "Suspected non-PD" as their Diagnosis on the subject's "Patient Data Collection Sheet". The reviewer specifically requests this because Study #16, a publication of clinical follow-up results of patients who had negative F-18 FDOPA PET in Study #15, states that "*A total of 185 parkinsonian patients were referred to the PET Center at North Shore University Hospital by movement disorders specialists to confirm a clinical diagnosis of PD. This diagnosis was entertained because of the presence of at least two cardinal features of disease (bradykinesia, rigidity, tremor, and/or gait disorder).*" Therefore based on the publication (Study #16) all 185 patients (including the 27 patients with negative F-18 FDOPA PET) referred to Feinstein Institute (North Shore University Hospital) had pre-imaging clinical diagnosis of "PD". However based on the applicant's "Patient Data Collection Sheet", the 27 patients who had negative F-18 FDOPA PET all had pre-imaging clinical diagnosis of "Suspected non-PD". This apparent discrepancy can only be resolved with FDA OSI inspection of the applicant's source records.

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It should be noted that "Suspected non-PD" is a clinical suspicion rather than a patient's standard of truth. Clinical follow-up or verification by other established methods would be needed to ascertain that a patient indeed does not have Parkinson Disease, hence can be given "non-PD" as the standard of truth. Similarly a patient's pre-imaging clinical suspicion of "PD" also needs to be verified by clinical follow-up or other established methods.

The applicant used patient's pre-imaging clinical diagnosis as the standard of truth and apparently demonstrated that F-18 FDOPA PET results were 100% identical to each patient's pre-imaging clinical diagnosis. Another regulatory problem then arises – if F-18 FDOPA PET simply duplicates each patient's pre-imaging clinical diagnosis, it appears that F-18 FDOPA PET provides no additional clinically useful information. This would particularly be true for the patients whose pre-imaging clinical diagnosis was already "PD" – what clinically useful information does F-18 FDOPA PET add? One of the important regulatory considerations in evaluating the efficacy of a diagnostic radiopharmaceutical is an assessment of the drug's ability to provide clinically useful information.

On 12/28/2012, the FDA review team expressed these concerns in its Day 74 Letter (filing letter) to the applicant:

1. *The clinical protocol describes a study in which patients with movement disorders were to undergo positron emission tomography (PET) imaging to estimate cerebral blood flow, brain glucose metabolism and brain fluorodopa uptake. The study design appears to represent an exploratory study since the protocol lacked a statistical analytical plan, including a primary endpoint for hypothesis testing. Hence, the results discussed in the marketing application appear to represent post-hoc analyses of exploratory clinical data where the pre-imaging clinical diagnosis was used as a standard of truth.*

2. *The use of a pre-imaging clinical diagnosis as a standard of truth suggests that, in this study, FDOPA imaging was incapable of estimating the ability to which the imaging could provide clinically useful information. The study showed FDOPA imaging results that were apparently identical to the pre-imaging clinical diagnosis; hence, the FDOPA imaging results suggest that imaging provided no clinically useful information. One of the important considerations in evaluating the efficacy of a diagnostic radiopharmaceutical is an assessment of the drug's ability to provide clinically useful information. The FIMR clinical study results appear useful in the generation of exploratory data but the results do not appear to support the ability of FDOPA imaging to provide clinically useful information.*

6.1.4 Analysis of Secondary Endpoints(s) - Comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls (Study #21)

I-123 FP-CIT SPECT (DaTscan) is approved in the U.S. and Europe. Its chemical name is N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[123I]iodophenyl)nortropane. FP-CIT selectively binds to dopamine transporter (DaT), and is approved to image dopamine transporter (DaT):

> *DaTscan is indicated for striatal dopamine transporter visualization by SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to Parkinsonian Syndrome (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy)*

Study #21 is a publication of an exploratory study comparing the sensitivity and specificity of I-123 FP-CIT SPECT vs. F-18 FDOPA PET. The study is a single center study conducted in the Europe. The study evaluated 11 early-stage Parkinson Disease (PD) patients, 17 advanced-stage PD patients, and 20 age-matched controls. Each of the PD patients in the study underwent both I-123 FP-CIT SPECT and F-18 FDOPA PET. Each control subject had either I-123 FP-CIT SPECT or F-18 FDOPA PET (10 in each group). All patients were followed for 1 year after the scans, and the follow-up clinical diagnosis was used as the standard of truth.

All study patients had strong clinical evidence of having Parkinson Disease:

- Criteria for early-stage PD:
  - strong clinical evidence of PD based on two of the three cardinal symptoms (rest tremor, bradykinesia, and rigidity)
  - disease duration of less than 3 years
  - were not using antiparkinson medication
- Criteria for advanced-stage PD:
  - two of the three cardinal symptoms
  - disease duration of 5–15 years
  - were using antiparkinson medication with a documented response

Twenty-nine (29) patients were recruited, underwent I-123 FP-CIT SPECT and F-18 FDOPA PET, and followed clinically for one year. Twenty-eight (28) patients had PD as SOT by clinical follower up and were included in the analysis. One patient did not respond to symptomatic antiparkinsonian medication and did not show worsening of extrapyramidal signs after a period of 3 years of clinical follow-up, and this patient was excluded from analysis. Patients with atypical signs, psychiatric disorders, signs of severe cognitive deterioration, severe cardiovascular co-morbidity or on medication known to interfere with dopamine transporters (DaT) or catechol-O-methyltransferase inhibitors were excluded.

Reviewer's comments: The study has a number of limitations. The study is a small single center study. All study patients had strong clinical evidence of PD, and patients with atypical signs and symptoms were excluded. However, in clinical practice, patients with strong clinical evidence of PD with documented response to antiparkinson medication may not benefit from another

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diagnostic imaging test, either I-123 FP-CIT SPECT or F-18 FDOPA PET. Patients with atypical signs and symptoms could potentially benefit from a diagnostic imaging test such as I-123 FP-CIT SPECT or F-18 FDOPA PET, but these patients were excluded from the study. The study is exploratory in nature with no hypothesis testing.

DaTscan labeling dosing recommendation is 111-185 MBq (3-5 mCi). In the study, each patient received 185 MBq DaTscan. In addition, each patient was injected 200 MBq F-18 FDOPA intravenously, and had 2.5 mg/kg carbidopa given orally one hour prior to F-18 FDOPA injection. Key parameters of the study are summarized in Table 5:

Table 5: STUDY #21 - Direct Comparison of FP-CIT SPECT and F-DOPA PET

Study Center	Number of Study Centers	Design and Control	Drug Dosage and Route	Study Objective	Number of Subjects included/ Completed	Duration	Gender M/F	Diagnosis	Primary Endpoint
University of Groningen	One	Static Study	1) 2.5mg/kg carbidopa (Oral) 2) 200 MBq FDOPA by IV 3) 185 MBq of DaTscan by IV	Compare the sensitivity and specificity of FDopa with DatScan	49/48	One day study followed by one year follow up study	34/14	Parkinsonian syndromes	Visual detection of putamen and caudate for loss or no loss of dopaminergic neurons

Data Analysis

Quantitative F-18 FDOPA uptake analysis was conducted by computing the Striatal Occipital Ratio (SOR) of bilateral caudate and putamen. Average SOR of caudate and putamen was used to calculate mean whole striatal SOR on each side. Scans considered abnormal when the SORs were less than the mean values minus 2 SD of the healthy controls. Sensitivity and Specificity was calculated for various brain regions: contralateral putamen, ipsilateral putamen, contralateral caudate, ipsilateral caudate, contralateral striatum, and ipsilateral striatum. Results of data analysis are shown in Table 6.

Table 6: Sensitivity and specificity based on uptake values

	Region	FP-CIT			F-DOPA		
		Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC
Early-stage versus controls	Contralateral caudate	91	100	0.98	91	90	0.95
	Ipsilateral caudate	82	90	0.86	64	90	0.80
	Contralateral putamen	100	100	1.00	100	100	1.00
	Ipsilateral putamen	100	100	1.00	91	90	0.95
	Contralateral striatum	100	100	1.00	100	100	1.00
	Ipsilateral striatum	73	100	0.95	82	90	0.92
All patients versus controls	Contralateral caudate	100	91	0.98	90	96	0.98
	Ipsilateral caudate	100	82	0.94	90	86	0.91
	Contralateral putamen	100	100	1.00	100	100	1.00
	Ipsilateral putamen	100	96	0.99	100	89	0.98
	Contralateral striatum	100	100	1.00	100	100	1.00
	Ipsilateral striatum	100	86	0.98	90	93	0.97

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Reviewer's comments: It should be noted in the above table that in calculating 'sensitivity' and 'specificity', definition of a 'positive scan' was arbitrarily set as an uptake value two standard deviations below the mean uptake (mean SOR) of healthy control, i.e. scans were considered abnormal when the SORs were less than the mean values minus 2 SD of the healthy controls. The arbitrary definition of 'positive scan' is another limitation of the study, and further exemplifies the study's exploratory nature. Furthermore, each patient in the analysis was confirmed to have PD via clinical follow-up, which serves as the standard of truth. It is unclear to the reviewer how 'specificity' was calculated, which involves true negatives, and it is unclear whether true negatives were simply healthy controls in the study.

It should also be noted that DaTscan is indicated to differentiate essential tremor from tremor due to Parkinsonian syndromes. The study did not include patients with essential tremor. Data in the above table appear to suggest that I-123 FP-CIT SPECT and F-18 FDOPA PET have comparable performance characteristics in a patient population with strong clinical evidence of PD. However due to the exploratory nature of the study, this conclusion needs further verification and support from other confirmatory clinical studies.

6.1.5 Other Endpoints

The applicant conducted quantitative analyses based Striatal Occipital Ratio (SOR) in normal controls (Table 7), patients with loss of dopaminergic neurons (Table 8), and compared SOR values between normal subjects and patients with negative F-18 FDOPA PET (Table 9). The reviewer considers (b) (4)

Table 7: SOR Values calculated for Normal Controls

	SOR PUTAMEN L LOW HIGH	SOR PUTAMEN R LOW HIGH	SOR CAUDATE L LOW HIGH	SOR CAUDATE R LOW HIGH
	(b) (4)			
MEAN	2.5452	2.5466	2.5886	2.6355
SD	0.1297	0.1520	0.1755	0.1753

Table 8: SOR Values calculated for Patients with Loss of Dopaminergic Neurons

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	SOR PUTAMEN L LOW HIGH	SOR PUTAMEN R LOW HIGH	SOR CAUDATE L LOW HIGH	SOR CAUDATE R LOW HIGH
	(b) (4)			
MEAN	1.6854	1.6698	2.0185	2.1056
SD	0.1232	0.1964	0.1947	0.2258

Table 9: SOR Values for Normal Subjects Compared to Patients with Negative F-18 FDOPA PET

	Normal Subjects (n=11)	Patients with a Negative PET Scan (n=27)
Mean SOR (Putamen)	2.5452	2.4781
Standard Deviation	0.1297	0.1559

The primary efficacy analysis of the clinical study conducted by the applicant (Study #15) used binary F-18 FDOPA PET reading methodology, i.e. either positive or negative. The applicant also analyzed severity of dopaminergic neuronal Loss (Table 10). The reviewer (b) (4)

Table 10: Criteria for Positive Scans to Indicate Severity of Dopaminergic Neuronal Loss

Classification	Criteria for the Classification
Positive +	Reduced uptake in one of the putamen and normal uptake on the other, as compared to normal scans
Positive ++	Significantly reduced uptake by the putamen bilaterally
Positive +++	Reduced uptake by the putamen bilaterally and reduced uptake by one of the caudate regions
Positive ++++	Reduced uptake by both the putamen and caudate bilaterally

6.1.6 Subpopulations

Study #16 "Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging" is a publication of clinical follow-up results on a subset of patients in Study #15. Patients (all had at least two cardinal features of Parkinson Syndromes) who had negative F-18 FDOPA PET were followed for a minimum of 2 years by movement disorder specialist to obtain patient's final clinical diagnosis. Based on Module 2 of the NDA, "eight patients that were not responding to PD treatment despite showing parkinsonian symptoms were selected to undergo Fludeoxyglucose F 18 PET scans". A clinical follow up (average 3.1 ±0.9 years) after the FDG metabolic studies on the eight patients did not show any signs of classical PD. Further clinical

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diagnosis indicated that they had either potential psychogenic movement disorder (n=3), DOPA responsive dystonia (n=2), lithium exposure, post-viral parkinsonian syndrome (n=1), or midbrain compression due to a cyst (n=1).

Reviewer's comments: As commented above, there is an apparent discrepancy of the pre-imaging clinical diagnosis of the F-18 FDOPA PET negative patients studied in this publication. The publication states that "A total of 185 parkinsonian patients were referred to the PET Center at North Shore University Hospital by movement disorders specialists to confirm a clinical diagnosis of PD. This diagnosis was entertained because of the presence of at least two cardinal features of disease (bradykinesia, rigidity, tremor, and/or gait disorder)", therefore all the F-18 FDOPA PET negative patients in this follow-up study should have pre-imaging clinical diagnosis of "PD". However based on the applicant's patient level data ("Fluorodopa Patient Data FDA"), all the 27 patients who had negative F-18 FDOPA PET had pre-imaging clinical diagnosis of "Suspected non-PD". The reviewer has requested the FDA Office of Scientific Investigation to inspect the applicant's source records to resolve this apparent discrepancy.

Based on the publication, none of followed patients developed clinical signs of classical PD or of an atypical parkinsonian syndrome at a follow-up visit conducted 3 years after imaging. However it was not clear as to how many of the 27 patients who had negative F-18 FDOPA PET were followed, and how many had final clinical diagnosis verified as "non-PD".

On 3/25/2013 the FDA review team held a Post-Midcycle Communication teleconference with the applicant. The following are clinical discussion summaries from the meeting minutes:

FDA asked the applicant to clarify the following two items:

1. *In reference to the study listed as #15 and #16, it is not clear whether only 27 or all 185 patients have not been responding to the anti-Parkinson therapy prior to undergoing an FDOPA scan.*
2. *In reference to the study #16, please clarify how many patients, out of 27, had a follow-up clinical diagnosis. In the application, such data are provided for only eight patients.*

Dr. Chaly responded that 27 patients were not responding to anti-Parkinson medications, while the rest (158 patients) were responding to anti-Parkinson medications upon referral to the Feinstein Institute for F-18 FDOPA PET. A clinical study coordinator at the Feinstein Institute held telephone conversations with referring physicians and designated each referred patient as "Parkinson Disease" or "Suspected Non-Parkinson" based on the telephone conversation. No additional records of the telephone conversation were kept. The coordinator was the only one at the Feinstein Institute who had knowledge of the clinical status/diagnosis of each referred patient, and the coordinator retired in 2006. All patients included in the F-18 FDOPA NDA were from 2006 or earlier.

Regarding the follow-up of the 27 patients who had negative F-18 FDOPA scans, Dr. Chaly was not able to confirm that all 27 patients were followed till final clinical diagnosis was confirmed. A visiting scholar (not present at the teleconference) to the Feinstein Institute

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was given the full responsibility of the follow-up of these 27 patients, and Dr. Chaly does not know all of the follow-up details.

Following the Post-Midcycle Communication teleconference, the applicant submitted another amendment to the NDA on 4/5/2013 to further clarify:

1) "In studies #15 and #16, 27 of the 185 patients were not responding to anti-Parkinson therapy prior to undergoing an FDOPA scan. These 27 patients were classified as "suspected non-PD" due to the fact that they exhibited parkinsonian symptoms but were not responding to treatment. They were referred to our center for a FDOPA scan in order to confirm that their symptoms were due to an ailment other than Parkinson's disease. The remaining 158 patients were responding to Parkinson's treatment and were classified as "PD".

2) Out of the 27 patients referred to in study #16, ten were contacted for follow up studies. Of the ten that were contacted, two were unavailable for unknown reasons. The follow-up study was conducted by Dr. Eckert and involved contacting the referring physicians within the time frame given in his publication (Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging: Thomas Eckert, MD et.al, Movement Disorders, Volume 22, No 2, pp 167-173, 2007). All eight patients had Fludeoxyglucose F 18 PET scans at some point during the study to check for atypical Parkinson's conditions. The Fludeoxyglucose F 18 PET scans of these eight patients did not disclose patterns of regional metabolic change compatible with classical PD or an atypical parkinsonian variant. None of these patients developed clinical signs of PD or an atypical parkinsonian syndrome at a follow-up visit conducted 3 years after imaging. The clinical diagnoses of these patients at follow up were varied, but included such disorders as potential psychogenic movement disorder, medication side effects, DOPA-responsive dystonia, lithium exposure, postencephal viral infection and midbrain compression secondary to a posterior fossa cyst.

Based on the applicant's clarification in the 4/5/2013 amendment to the NDA, the regulatory question of clinical utility again comes to surface. It appears that 158 of the 185 patients who were referred to the Feinstein Institute for F-18 FDOPA PET already had a clinical diagnosis of Parkinson Disease based on the facts that 1) they all exhibited at least two of the cardinal features of Parkinsonian syndromes (dyskinesia, rigidity, tremor, and/or gait disorders), and 2) they were responding to antiparkinson medications. Then what clinically useful information does F-18 FDOPA PET provide to these patients? Code of Federal Regulations (21 CFR 315.5) states that "the effectiveness of a diagnostic radiopharmaceutical is assessed by evaluating its ability to provide useful clinical information related to its proposed indications for use." It appears F-18 FDOPA PET does not provide useful clinical information to patients who have pre-imaging clinical diagnosis of PD based on their clinical symptoms and the fact that they are responding to antiparkinson medications, and therefore F-18 FDOPA would not be indicated in these patients.

For the 27 patients who exhibit at least two cardinal features of Parkinson Disease but are not responding to antiparkinson medications, F-18 FDOPA PET could potentially provide useful clinical information, if the imaging test's accuracy/reliability could be confirmed by clinical data.

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The problem is that only 8 out of 27 such patients were clinically followed to obtain patient's final clinical diagnosis so as to allow verification of the accuracy of the imaging test F-18 FDOPA PET. The other 19 patients who could potentially benefit from an imaging test such as F-18 FDOPA PET unfortunately were not followed, and therefore these patients did not have their standard of truth (final clinical diagnosis) established to allow for assessment of the accuracy of the imaging test F-18 FDOPA PET.

Overall the clinical reviewer concludes that a patient population who exhibit at least two cardinal features of Parkinsonian syndrome but are not responding to antiparkinson medication could potentially receive useful clinical information from an imaging test such as F-18 FDOPA PET, however clinical data to verify the accuracy/reliability of the imaging test F-18 FDOPA PET are scarce – in this case only 8 such patients with verified standard of truth to allow for the assessment of the performance characteristics of F-18 FDOPA PET.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Different clinical studies in the application used different F-18 FDOPA and carbidopa pretreatment dosing. Table 11 compares various dosing regimens used in six clinical studies of the application. The FDA Clinical Pharmacology review team has reviewed the proposed F-18 FDOPA dosing regimen including the dosing regimen for carbidopa pretreatment and found the proposed dosing for F-18 FDOPA ((b) (4) 5 mCi intravenous injection) and carbidopa pretreatment (150 mg given orally one hour prior to F-18 FDOPA injection) acceptable.

Table 11: F-18 FDOPA and Carbidopa Dosing Used in Six Clinical Studies of the NDA

Study #	Number of Subjects	Mean Age (years)	Fluorodopa F 18 Injection Dose	Adverse Events
15	196	Controls: 51±13 Patients: 53±9	4-5 mCi (148-185 MBq) (150 mg carbidopa)	None
17	35	67.4±5.2	180 MBq (100 mg carbidopa)	None
18	45	61±9.8	110-200 MBq	None
19	186	N/A	150-180 MBq (150 mg carbidopa)	None
21	48	Early PD: 51.3 Advanced PD: 64.5 Control: 60.2	200 MBq (2.5 mg/kg carbidopa)	None
22	110	Patient: 63.8 Control: 60.3	172 MBq (150 mg carbidopa)	None

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7 Review of Safety

Safety Summary

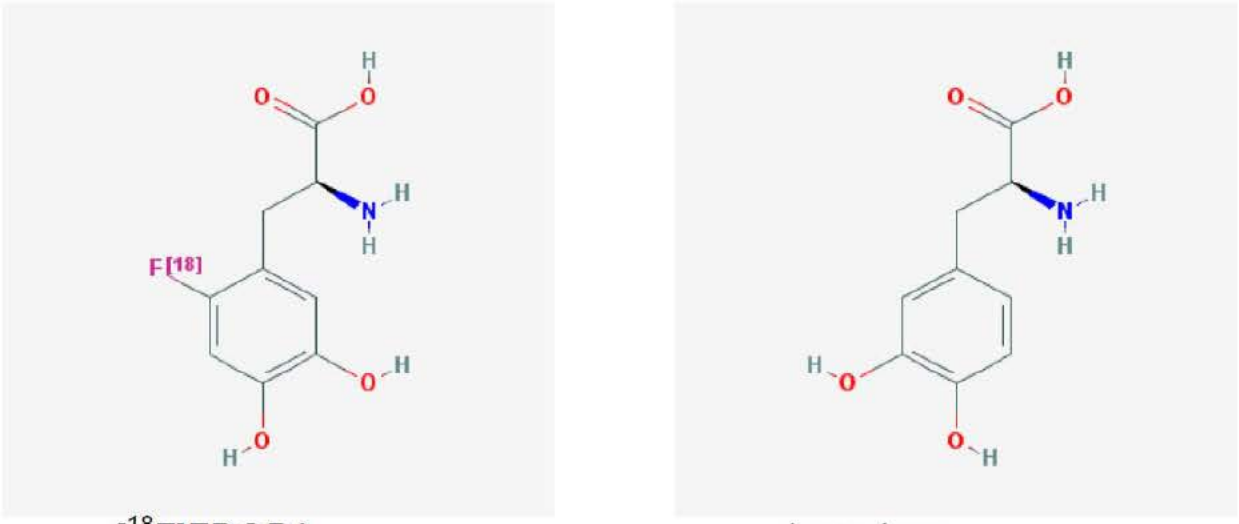
The NDA re-submitted at the beginning of the NDA review cycle (October 22, 2012) contain no safety data. The applicant states in the submission:

> *"No serious or significant adverse events have been reported due to the administration of Fluorodopa F 18 Injection. Generally, compounds belonging to the aromatic amino acid structural class are considered to be safe. The extremely small mass amount of the active ingredient present in the drug product has no therapeutic effect and therefore would not be expected to have any toxicity. In addition, the majority of the metabolites are eliminated from the body within 24 hours through the bladder."*

Following the FDA communication on potentially filing deficiencies of the NDA, the applicant submitted as an amendment to the NDA patient level data for the clinical study conducted by the applicant. The spreadsheet containing patient level data of the study contains a column for "Adverse Events", and all 196 subjects of the study had no adverse events based on the spreadsheet.

F-18 FDOPA is structurally similar to levodopa, with the only difference between the two being F-18 labeling at position 6 of the aromatic ring (Figure 3)

Figure 3: Structural Comparison of F-18 FDOPA and Levodopa



Based on FDA CMC review, the calculated total mass of F-19 fluorodopa, based on a specific activity of > (b) (4) mCi/mmol, ranges from (b) (4) to (b) (4) mg, depending on the yield of from (b) (4) mCi of product. This corresponds roughly to (b) (4) mg FDOPA/mL of product. This is smaller than the mass dose often used for levodopa, which in clinical practice could be over (b) (4) mg

daily. The reviewer considers F-18 FDOPA in the proposed single administration dosing, does not pose additional safety concerns.

8 Pediatric Research Equity Act (PREA) Requirements

The applicant initially submitted a request for deferring pediatric studies assessing the safety and effectiveness of Fluorodopa F 18 Injection in pediatric patient. Subsequently the applicant acknowledged that this deferral request submitted with the NDA was a mistake, and the applicant submitted a full pediatric waiver as an amendment to the NDA on 1/3/2013.

The applicant states that Fluorodopa F 18 Injection is not intended for pediatric patients. The proposed indication for Fluorodopa F 18 injection has extremely limited applicability to pediatric patients because of the pathophysiology of Parkinson's disease, which is found mostly in adult population. Studies with Fluorodopa F 18 Injection would be impossible or highly impractical for pediatric patients as the indication relates to the adult-related condition of Parkinson's Disease. The reviewer agrees with the applicant's rationale and recommends granting the applicant's request for a full pediatric waiver.

On June 5, 2013, the FDA Pediatric Review Committee (PeRC) discussed the application and agreed with granting full pediatric waiver.

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9 Appendices

9.1 Midcycle Presentation

Reference ID: 3329568

U.S. Food and Drug Administration
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Fluorodopa F-18 Injection Midcycle Presentation

Brenda Ye, M.D.
DMIP Medical Officer

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Regulatory History

- FDA Public Meeting 7/28/2000
  - Available literature data insufficient to support efficacy in any patient population
- Pre-IND: 2008
- Original NDA submission: 10/29/2009
  - PDUFA start date: 1/ 21/2010 (date user fee waiver granted)
- Refuse to File: 3/19/2010
- Expanded Access IND: 6/21/1012
- NDA Resubmission: 10/22/2012

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Proposed Indication

- Fluorodopa F 18 Injection is a [redacted (b) (4)] used in Positron Emission Tomography (PET) to visualize dopaminergic [redacted (b) (4)] in the striatum in adult patients with suspected parkinsonian syndromes (PS). [redacted (b) (4)] Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.

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Reports of Efficacy and Safety Studies (Studies #15-23)

- Reports of 'Controlled' Clinical Studies (2)
- Reports of Uncontrolled Clinical Studies (2)
- Reports of Analyses of Data From More Than One Study (2)
- Other Study Reports (3)

- 1 'controlled' study by the Applicant, 8 publications

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Reports of Efficacy and Safety Studies (Studies #15-23)

- Reports of 'Controlled' Clinical Studies
  - STUDY #15: Clinical Study of Fluorodopa F 18 Injection Conducted by Feinstein Institute
    - Conducted by the Applicant, patient-level data submitted to the NDA
  - STUDY #16: Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging
    - Publication of a follow-up study on a subset of patients in Study #15

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Reports of Efficacy and Safety Studies (Studies #15-23)

- Reports of Uncontrolled Clinical Studies
  - STUDY #17: Striatal and Extrastriatal Dysfunction in Parkinson's Disease with Dementia: A 6-[18F]Fluoro-L-Dopa PET Study
    - Publication of an exploratory study analyzing FDOPA influx constant (Ki) in various brain regions
  - STUDY #18: A Comparison of the Progression of Early Parkinson's Disease in Patients Started on Ropinirole or L-Dopa: An 18F-Dopa PET Study
    - Publication of an exploratory study on disease progression (all patients were diagnosed with Parkinson Disease) and treatment response (to Ropinirole vs L-Dopa)

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Reports of Efficacy and Safety Studies (Studies #15-23)

- Reports of Analyses of Data From More Than One Study
  - STUDY #19: Slower Progression of Parkinson's Disease with Ropinirole versus Levodopa: The REAL-PET Study
    - Publication of a clinical study designed to compare treatment response to ropinirole vs. L-dopa; all patients recruited patients were already diagnosed with PD
  - STUDY #20: A Technique for Standardized Central Analysis of 6-Fluoro-L-Dopa PET from Multicenter Study
    - Publication of technical portion of Study #19

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Reports of Efficacy and Safety Studies (Studies #15-23)

- Other Study Reports
  - STUDY #21: Direct Comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls
    - Publication of an exploratory study comparing sensitivity and specificity of DaTscan and FDOPA
  - STUDY #22: Simple Ratio Analysis of 18F-Fluorodopa Uptake in Striatal Subregions Separates Patients with Early Parkinson Disease from Healthy Controls
    - Publication of an exploratory study assessing whether a simple ratio analysis (SOR) of FDOPA uptake in various brain regions would reliably separate PD patients from healthy controls
  - STUDY #23: Fluorine-18-Fluoro-L-DOPA Dosimetry with Carbidopa Pretreatment
    - Publication of an exploratory study showing the effect of carbidopa pretreatment on FDOPA biodistribution and dosimetry.

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Relevant Clinical Studies

- STUDY #15/16 ('Controlled' Study): The Study Conducted by The Feinstein Institute for Medical Research

Study #15	The Feinstein Institute	Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research	
Study #16	Eckert, et. al.	Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging	*Movement Disord* 2007;22:167-173

- STUDY #21(Other Study): Direct Comparison of FP-CIT SPECT and F-DOPA PET

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Clinical Study #15/16
The Feinstein Study

- Retrospective single center study - conducted by the applicant on site at the Feinstein Institute
- Enrollment Criteria – "All patients were referred by a movement disorder physician and exhibited at least two of the cardinal features of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder)"
- Study subjects: 196 total
  - 185 patients referred to Feinstein Institute for FDOPA PET
  - 11 normal controls

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Clinical Study #15/16 The Feinstein Study

- Patients' initial clinical diagnosis as SOT
  - 'Parkinson Disease' (PD): 158 patients [data listing]
  - 'Suspected non-PD': 27 patients [data listing]
  - * Publication (Study #16): all 185 referred to Feinstein by movement disorders specialists to confirm a clinical diagnosis of PD (presence of at least two cardinal features of PD: bradykinesia, rigidity, tremor, and/or gait disorder)
- Study Drug Dosing: 4-5 mCi intravenous
  - Patient Preparation: 150 mg carbidopa po an hour before F-18 FDOPA injection to block peripheral decarboxylation of FDOPA

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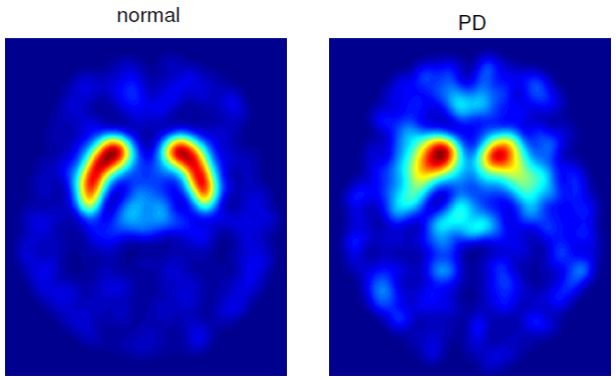
F-18 FDOPA PET Reading Methodology: Binary Read

- Negative scan - uniform uptake of FDOPA bilaterally by caudate and putamen (crescent-shaped caudate and putamen bilaterally)
- Positive scan – reduced uptake of FDOPA by putamen or putamen/caudate, either unilaterally or bilaterally
  - Putamen often affected earlier and more severely than caudate as PD progresses

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Sample F-18 FDOPA PET Images



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Clinical Study #15/16
The Feinstein Study: Results

FDOPA PET Results	Clinical Diagnosis			
	Control	PD	Suspected non-PD	Total
Positive		158		158
Negative	11		27	38
Total	11	158	27	196

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Study #16: Follow-up of F-18 FDOPA PET Negative Patients

- STUDY #16: Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging
- 27 patients with negative F-18 FDOPA PET were followed for a minimum of 2 years by movement disorder specialist
- All patients were referred by a movement disorder physician and exhibited at least two of the cardinal features of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder)
  - 27 “suspected non-PD” (exhibit Parkinsonian symptoms but not responding to antiparkins medications) in Module 5 summary and patient data spreadsheet but not according to the publication

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Study #16: Results

- Analysis of putamen uptake ratios: SOR values were within the normal range
- Average age of 45 ±19 years
- None had classical PD or atypical degenerative forms of Parkinsonism based on follow-up

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Study #16: Results

- The final clinical diagnoses for these patients included secondary forms of parkinsonism such as vascular, psychogenic or drug induced tremor, including
  - potential psychogenic movement disorder (n=3)
  - DOPA responsive dystonia (n=2)
  - lithium exposure
  - post-viral parkinsonian syndrome (n=1)
  - midbrain compression due to a cyst (n=1)

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Study #16: Follow-up of F-18 FDOPA PET Negative Patients

Patient Age Profile

Characteristic	NEG-PD (n=27)	NORMALS (n=11)	POS-PD (n=158)	p-Value
Age (years)**	45.30±19.32 (42; 17-86)	58.64±15.21 (68; 34-72)	56.75±12.47 (54.5; 16-81)	<.0003
%Male	16/27 (59.3%)	8/11 (72.7%)	91/158 (57.6%)	NS p<.61

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Feinstein Study Deficiencies

- Single Center retrospective study
- Patient's initial clinical diagnosis upon referral to Feinstein Institute for FDOPA scan as the Standard of Truth
  - Study drug lacks clinical utility if patient's diagnosis is already clear
  - For patients who were *suspected* of Parkinson Disease, there is no further follow-up of most patients to confirm patient's clinical diagnosis (only patients with negative FDOPA PET were followed)

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Feinstein Study Deficiencies

- Although 27 FDOPA PET negative patients were followed for ≥2 year to obtain patient's true clinical diagnosis, there is age difference between FDOPA PET positive patients and FDOPA PET negative patients
  - raising the question whether the difference in FDOPA PET results could largely be explained by age difference

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Relevant Clinical Studies

- STUDY #15/16 ('Controlled' Study): The Study Conducted by The Feinstein Institute for Medical Research

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Study #16	Eckert, et. al.	Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging	*Movement Disord* 2007;22:167-173

- STUDY #21(Other Study): Direct Comparison of FP-CIT SPECT and F-DOPA PET

I-123 FP-CIT SPECT (DaTscan)

N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-[123I]iodophenyl)nortropane

- Approved in the U.S. and Europe
- Selectively binds to dopamine transporter (DaT) => DaT imaging agent
- Indicated for striatal dopamine transporter visualization by SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to Parkinsonian Syndrome (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy)
- Recommended dosing: 111 to 185 MBq (3 to 5 mCi)

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Clinical Study #21

F-18 FDOPA PET vs. I-123 DaTscan SPECT

- Single center study in Europe
- Inclusion: patients with strong clinical evidence of having Parkinson's disease
- Exclusion: patients with atypical signs, psychiatric disorders, signs of severe cognitive deterioration, severe cardiovascular co-morbidity or on medication known to interfere with dopamine transporters (DaT) or catechol-O-methyltransferase inhibitors

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Clinical Study #21: Study Patients

F-18 FDOPA PET vs. I-123 DaTscan SPECT

- 29 patients recruited
  - 28 patients included in analysis
    - 11 early-stage patients:
      - strong clinical evidence of PD based on two of the three cardinal symptoms (rest tremor,bradykinesia and rigidity)
      - disease duration of less than 3 years
      - were not using antiparkinson medication
    - 17 advanced-stage patients
      - two of the three cardinal symptoms
      - disease duration of 5–15 years
      - were using antiparkinson medication with a documented response

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Clinical Study #21

F-18 FDOPA PET vs. I-123 DaTscan SPECT

- One patient was excluded (patient did not respond to symptomatic antiparkinsonian medication and did not show worsening of extrapyramidal signs after a period of 3 years of clinical follow-up)
- 20 controls (10 FDOPA + 10 DaTscan)
- SOT - All patients were followed for 1 year after the scans: 28 PD, 1 without PD excluded

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Clinical Study #21

F-18 FDOPA PET vs. I-123 DaTscan SPECT

- Each of the 28 patients had both FDOPA PET and DaTscan SPECT
- 20 controls either FDOPA PET or DaTscan SPECT
- Study Drug Dosing
  - 2.5 mg/kg carbidopa PO 1 hr prior to FDOPA
  - 200 MBq F-18 FDOPA IV
  - 185 MBq DaTscan IV

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Clinical Study #21: Data Analysis

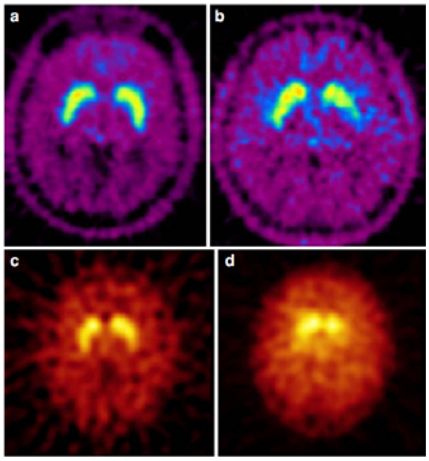
F-18 FDOPA PET vs. I-123 DaTscan SPECT

- SOR of caudate and putamen
- Average SOR of caudate and putamen to calculate mean whole striatal SOR
- Scans considered abnormal when the SORs were less than the mean values minus 2 SD of the healthy controls
- Sens and Spec based on each brain region – contralat/ipsilat putamen, caudate, striatum
- ROC produced

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Sample Images: FDOPA PET vs DaTscan



- a – FDOPA PET in healthy control
- b - FDOPA PET in early-stage PD
- c – DaTscan in healthy control
- d – DaTscan in early-stage PD

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Clinical Study #21

F-18 FDOPA PET vs. I-123 DaTscan SPECT

Patients Demographics

	Controls		Early-stage patients		Advanced-stage patients	
	FP-CIT	F-DOPA	FP-CIT	F-DOPA	FP-CIT	F-DOPA
No. of subjects	10	10	11	11	17	17
Men	5	5	8	8	15	15
Women	5	5	3	3	2	2
Age (years)						
Mean	60.2	61.4	51.3	51.3	64.5	64.5
SD	8.7	8.5	10.1	10.1	6.3	6.3

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Clinical Study # 21

F-18 FDOPA PET vs. I-123 DaTscan SPECT

Results: Early-Stage PD vs. Controls

Brain Regions	Sens (DaTscan)	Sens (FDOPA)
Contral. Putamen	100	100
Ipsil. Putamen	100	91
Contral Caudate	91	91
Ipsil. Caudate	82	64
Contral. Striatum	100	100
Ipsil. Striatum	73	82

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Clinical Study # 21

F-18 FDOPA PET vs. I-123 DaTscan SPECT

Results

	Region	FP-CIT			F-DOPA		
		Sensitivity (%)	Specificity (%)	AUC	Sensitivity (%)	Specificity (%)	AUC
Early-stage versus controls	Contralateral caudate	91	100	0.98	91	90	0.95
	Ipsilateral caudate	82	90	0.86	64	90	0.80
	Contralateral putamen	100	100	1.00	100	100	1.00
	Ipsilateral putamen	100	100	1.00	91	90	0.95
	Contralateral striatum	100	100	1.00	100	100	1.00
	Ipsilateral striatum	73	100	0.95	82	90	0.92
All patients versus controls	Contralateral caudate	100	91	0.98	90	96	0.98
	Ipsilateral caudate	100	82	0.94	90	86	0.91
	Contralateral putamen	100	100	1.00	100	100	1.00
	Ipsilateral putamen	100	96	0.99	100	89	0.98
	Contralateral striatum	100	100	1.00	100	100	1.00
	Ipsilateral striatum	100	86	0.98	90	93	0.97

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Clinical Study #21 Limitations

- Single center study
- All study patients had strong clinical evidence of PD, and these patients may not need another imaging test to confirm diagnosis
  - Patients with atypical symptoms were excluded, but these are patients who may benefit from an imaging test in further diagnostic work-up

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Clinical Study #21 Limitations

- Exploratory study
- No blinded image read
- Calculation of Specificity unclear from the publication, even definitions of positive/negative scans are quantitative exploratory measures
- Small study

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Efficacy Summary

- 9 clinical studies submitted
- 2 studies relevant for evaluating diagnostic efficacy (performance characteristics) of FDOPA
- Both studies with serious deficiencies:
  - Study 15/16: retrospective, single center, initial clinical diagnosis as SOT (lacking clinical utility), most patients without true SOT
  - Study 21: exploratory, single center, all study patients already diagnosed with PD (not target patient population), definitions of positive/negative scans quantitative exploratory measures, unclear how specificity was calculated

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Safety Data

- No safety data submitted in the NDA
- Applicant states that there have been no safety concerns from over 20 years of use of the drug at the Feinstein Institute
- Derivative of L-dopa, which has a known safety profile

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Recommendations

- Complete Response based on lack of robust clinical data for efficacy
- Continue enrolling patients through the Expanded Access IND
  - of patients scanned with FDOPA PET, the applicant plans to follow 20-30 patients for 2-3 years to obtain standard of truth

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/s/

BRENDA Q YE
06/21/2013
Spelling errors corrected by the reviewer without changing contents of the review.

Summary of F18 Fluorodopa publications pertaining to use of the imaging drug in neurologic disease evaluation

NDA: 200655

Reviewer: Dwaine Rieves/Director/DMIP

Today's date: November 18, 2011

1. Summary:

The Division of Medical Imaging Products recently received an inquiry from Dr. Thomas Chaly requesting assistance in continuing to provide F18 fluorodopa (FDOPA) to patients at his institution. The division has had several interactions with Dr. Chaly over the past years, including a meeting where the division staff pointed out the lack of sufficient efficacy data from the publications he was citing to support the efficacy of FDOPA, relative to an NDA submission. In response, Dr. Chaly met with the division on July 19, 2010 where he noted that he desired to present certain data from his own institution to support the safety and efficacy of FDOPA.

At the July 19, 2010 meeting, Dr. Chaly outlined how, in his opinion, the FDOPA test has 100% sensitivity and 100% specificity. The division pointed out errors within his mathematics and also the inability to actually calculate performance criteria due to the lack of a truth standard (medical evidence deficit). The division reiterated the importance of Dr. Chaly obtaining medical assistance in the analysis and interpretation of his clinical data. Dr. Chaly stated that he has been unable to obtain assistance from medical doctors.

On November 9, 2011, Dr. Chaly sent a letter (email) requesting FDA assistance in order for him to continue providing FDOPA to his clinicians/patients after December 12, 2011. On November 17, 2011, the division talked with Dr. Chaly and encouraged him to submit an IND to support the continued use of FDOPA. The division emphasized that the staff would work expeditiously to review the IND and resolve any concerns such that the FDOPA use could continue uninterrupted. Dr. Chaly again noted that he has not been able to obtain any medical doctors to help him develop FDOPA and he has concerns that his institution's medical doctors will not have the time to help him. He expressed some hope that he could obtain a medical doctor's assistance as a sub-investigator in an IND study. Dr. Chaly also noted that he thought FDA should approve FDOPA since he has used it for many years with no problems and his medical doctors tell him the test is useful.

2. Purpose of this memorandum:

This review memorandum documents that we have once again examined the Pub Med listing of publications in order to determine if published data are sufficient to support the efficacy of FDOPA. As of this date, we continue to find a deficit of published information sufficient to support the approval of FDOPA as a diagnostic imaging agent

Reference ID: 3047573

for use in the care of patients with symptoms of Parkinson's Disease. The supplied exploratory information suggests some potential for FDOPA usefulness, although similar information is currently provided by DaTscan, a marketed SPECT drug.

The following timeline observations are relevant:

- 2000 FDA held a public discussion of FDOPA; observations at that time did not support the efficacy of FDOPA in clinical practice, although the potential for its use as a biomarker was noted.

- 2005 Publication of a systematic review of radiotracer imaging in Parkinson's disease that examined the published literature regarding FDOPA, C11-dihydrotetrabenazine, I123 beta-CIT SPECT (DaTscan) and F18FDG concluded that, "The four tracers fulfill this [biologic relevance] criterion, although they do not measure the number or density of dopaminergic neurons. Biomarkers used as diagnostic tests, prognostic tools, or surrogate endpoints must not only have biologic relevance but also a strong linkage to the clinical outcome of interest. No radiotracers fulfill these criteria and current evidence does not support the use of imaging as a diagnostic tool in clinical practice or as a surrogate endpoint in clinical trials." From: The role of radiotracer imaging in Parkinson's Disease; Neurology 2005: 64(2):208-15.

- 2006 American Academy of Neurology publishes "Practice Parameter: Diagnosis and Prognosis of New Onset Parkinson Disease (an evidence-based review);" this was a systematic review of all published reports from 1997 through 2002 based upon multiple database listings of publications. A standard evidence quality assessment was used to assess the usefulness of the information in the reports. The Academy concluded that no reports of FDOPA were conducive to review due to inability to meet study design and conduct quality expectations for a study. The Academy concluded "Beta-CIT and IBZM SPECT are possibly useful in distinguishing PD from ET and normals (five class III studies). There is insufficient evidence to determine if these modalities are useful in distinguishing PD from other forms of parkinsonism."

- 2008 Dr. Chaly submits results of his review of all publications (21) supporting the safety and efficacy of FDOPA. The review of this material by the Division (see PreIND 78861) found insufficient evidence of efficacy. Much of the submitted publications referred to therapeutic studies were FDOPA was explored for clinical evidence of an indicator of a therapeutic effect.

- 2009 Dr. Chaly submits copies of five additional publications that he regards as potentially useful to help evaluate FDOPA. The division's review (see PreIND 78861) noted multiple limitations within these data, mainly related to lack of an objective of diagnostic performance assessment.

- 2009 Dr. Chaly submits an NDA which contained the previously cited publications. An RTF letter was issued related to multiple deficiencies in data analyses, lack of safety and dosage data and lack of required NDA clinical components.

- 2009 GE Healthcare submits NDA for DaTscan (ioflupane I 123) Injection; was approved in January 2011 for: "striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to PS (idiopathic Parkinson's Disease, multiple system atrophy and progressive supranuclear palsy). DaTscan is an adjunct to other diagnostic evaluations." The safety and efficacy data were obtained from studies conducted by GE Healthcare.

- November, 2011 publication of "The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration" Brain 2011; 134(3146-3166). This publication describes in detail the diagnostic value of DaTscan and briefly mentions alternatives. It notes that a 2003 publication "found a generally similar imaging pattern between the two approaches "(FDOPA and DaTscan).

- November 18, 2011 I searched PubMed for all clinical trial publications for "fluorodopa PET" within the past 3 years. Below are the references/publications cited (the search was confined to clinical trials/did not include reviews):

- 1). Comparison of dopamine turnover, dopamine influx constant and activity ratio of striatum and occipital brain with F18 dopa in brain PET normal controls and patients with Parkinson's Disease. Eur J Nucl Med Mol Imaging. 2011 Aug:38(8); 1550-9.

- This study examined 9 healthy volunteers and 36 patients with Parkinson's Disease in order to estimate the "turnover" of dopamine within the brain. The study did not examine any diagnostic parameters. The study found dopamine "turn-over" was different between patients and controls.

- 2). Dopamine cell implantation in Parkinson's disease: long term clinical and F18 FDOPA PET outcomes. J Nucl Med 2010 Jan; 51(1):7-15.

- This study examined FDOPA uptake in the brains of 33 patients who had embryonic dopamine cell implantation for Parkinson's Disease. The study did not examine any diagnostic outcomes. The FDOPA observations suggested some transplanted cells were viable for up to four years after implantation.

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/s/

RAFEL D RIEVES
11/21/2011

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

PHARMACOLOGY/TOXICOLOGY NDA MEMO TO FILE

Application number:	200655
Supporting document/s:	505(b)(2) Class 2 Re-submission dated 12/15/15 FDA CR action letter dated – 10/22/13 Pharmacology/Toxicology NDA Review and Evaluation dated 6/10/2013
Product:	Fluorodopa F 18 Injection ([18F]FDOPA)
Indication:	Radioactive diagnostic agent developed for use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes
Applicant:	Fluorodopa F 18 Injection ([18F]FDOPA)
Review Division:	DMIP
Reviewer:	Sally J. Hargus, PhD
Supervisor/Team Leader:	Adebayo Laniyonu, PhD
Division Director:	Libero (Louis) Marzella, MD, PhD
Project Manager:	Thuy Nguyen, RPM

The Applicant re-submitted its NDA to respond to the FDA Complete Response (CR) Action. There were no pharmacology or toxicology issues in the CR letter. The Nonclinical Recommendation on the NDA is Approve, as discussed in the Pharmacology/Toxicology NDA Review and Evaluation, dated 10 June 2013. The NDA Review may be found in DARRTS.

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/s/

SALLY J HARGUS
04/13/2016

ADEBAYO A LANIYONU
04/13/2016

Supervisory Pharmacologist Memo

NDA: 200-655

Product: Fluorodopa F 18 Injection ([^{18}F]FDOPA)

Sponsor: Feinstein Institute for Medical Research

This memo to file is in respect of NDA 200-655 application for Fluorodopa F 18 Injection ([^{18}F]FDOPA) proposed as a radioactive diagnostic agent for use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes.

The sponsor did not submit any original nonclinical data for this 505(b)(2) NDA application. However, FDA conducted a review and evaluation of [^{18}F]FDOPA Injection in preparation for a 2000 Public Meeting between the FDA and the Clinical PET community. At the time, the available nonclinical information on [^{18}F]FDOPA, and the nonclinical and clinical literature on Levodopa were considered adequate to support nonclinical recommendation for clinical use of [^{18}F]FDOPA Injection for PET imaging studies. The sponsor cited the July 2000 public meeting to support the application.

Dr. Hargus conducted the Pharmacology/Toxicology primary review of the NDA. She concurred with the Agency's 2000 recommendation for approval from nonclinical perspectives. She deferred labeling recommendations.

I concur.

Adebayo Laniyonu, Ph.D.

Supervisory Pharmacologist

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/s/

ADEBAYO A LANIYONU
06/18/2013

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CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	200655
Supporting document/s:	NDA 200655; IND 78861
Applicant's letter date:	10/22/2012
CDER stamp date:	10/22/2012
Product:	Fluorodopa F 18 Injection ([^{18}F]FDOPA)
Indication:	Radioactive diagnostic agent developed for use with Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes.
Applicant:	Feinstein Institute for Medical Research 350 Community Drive Manhassett, NY 11030
Review Division:	Division of Medical Imaging Products, ODE IV, OND, CDER, US FDA
Reviewer:	Sally Hargus, PhD
Supervisor/Team Leader:	Adebayo Laniyonu, PhD
Division Director:	Louis Marzella, MD (Acting)
Project Manager:	Thuy Nguyen, MS

Template Version: September 1, 2010

The Drug Product is referred to as 'Fluorodopa F 18 Injection' or [^{18}F]FDOPA throughout this review.

Reference ID: 3322236

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1 Executive Summary

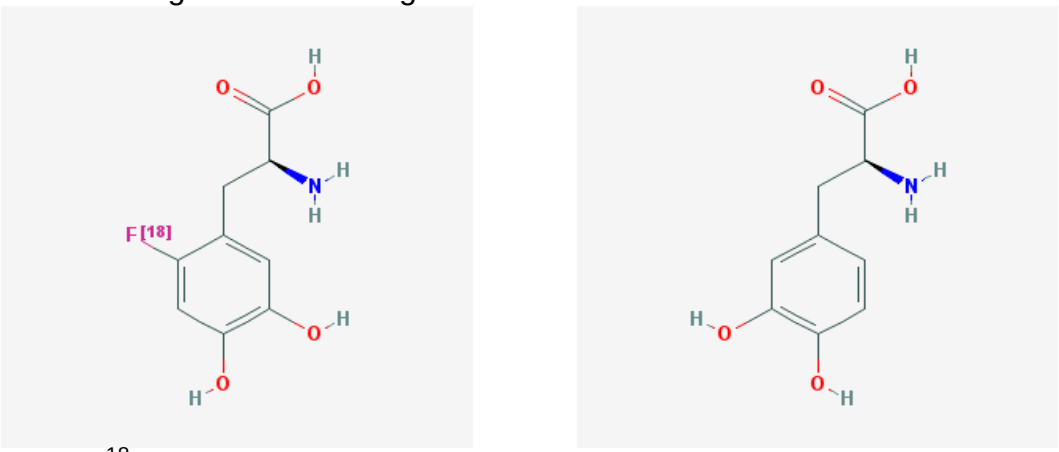
1.1 Introduction

NDA 200655 is a 505(b)(2) New Chemical Entity submission from Feinstein Institute for Medical Research for approval of "Fluorodopa F 18 Injection" ([18F]FDOPA), proposed as a Radioactive Diagnostic Agent in Positron Emission Tomography (PET). The proposed indication is to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes (PS).

1.2 Brief Discussion of Nonclinical Findings

FDA conducted a review and evaluation of [18F]FDOPA Injection in preparation for a Public Meeting in July 2000 between the FDA and the Clinical PET community. At the time, the available nonclinical pharmacology information on [18F]FDOPA, and the Pharmacology/Toxicology and clinical literature on Levodopa were considered adequate to support clinical use of [18F]FDOPA Injection for PET imaging studies (see attached review of [18F]FDOPA Paper NDA, by Adebayo. Laniyonu, Ph.D., Supervisory Pharmacologist, DMIP). The assessment was based upon the criteria listed below.

- [18F]FDOPA and Levodopa are nearly identical molecules. [18F]FDOPA contains a Fluorine atom (Fluorine-18) at the 6 position instead of a Hydrogen atom on the aromatic ring as shown in Figure 1.



[18F]FDOPA Levodopa

Figure 1. Structural Comparison of [18F]FDOPA and Levodopa.
Source of structures: http://ncbi.nlm.nih.gov

- The safety of Fluorodopa F 18 Injection is well supported in terms of historical use of Levodopa for treatment of Parkinson's disease.

- The availability of extensive nonclinical and clinical databases on Levodopa.

- The availability of a nonclinical pharmacology database on [18F]FDOPA.

- The safety of Levodopa is widely accepted at prescribed doses up to 2000 mg per day for chronic use (Carbidopa/Levodopa Monograph 2013), which is more than 1000-fold the one-time intravenously-administered [^{18}F]FDOPA mass dose of (b) (4) mg or less.

- The radiologic dose of Fluorodopa F 18 Injection, (b) (4) 5 mCi, is typically acceptable for diagnostic PET procedures, and presents a negligible risk of radiologic-based toxicity in adult patients.

No original nonclinical studies were submitted in support of NDA 200655, nor were original nonclinical studies required by FDA for the current submission.

1.3 Recommendations

1.3.1 Approvability

NDA 200655 is recommended for Approval from Pharmacology and Toxicology perspectives.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Labeling will be addressed in a separate review document.

2 Drug Information

2.1 Drug

CAS Number: 92812-82-3

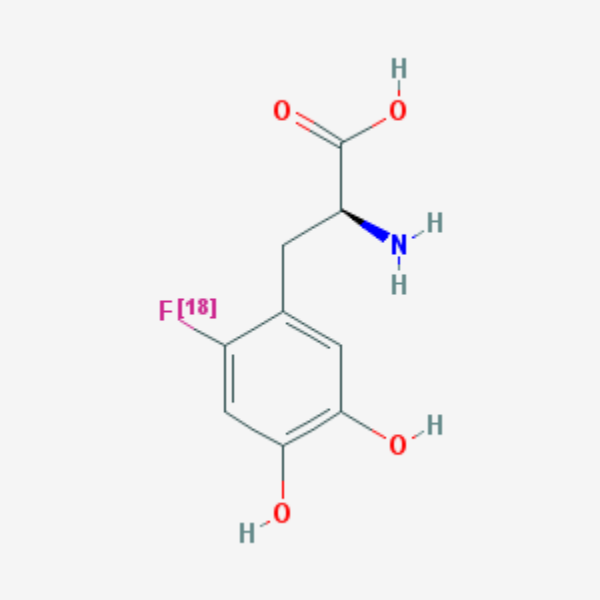
Generic Name: Fluorodopa F 18 Injection; [^{18}F]FDOPA

Chemical Name: 6-[^{18}F]Fluoro-L-3, 4-dihydroxyphenylalanine

Molecular Formula: $C_9H_{10}FNO_4$

Molecular Weight: 214.18 g/mol

Structure: [^{18}F]FDOPA



Source of structure: http://ncbi.nlm.nih.gov/

Pharmacologic Class: Radioactive diagnostic agent

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 78861 (Feinstein Institute)

FDA Paper NDA for [^{18}F]FDOPA, an FDA Internal Document authored by Dr. Adebayo Laniyonu in preparation for the July 2000 Public Meeting between FDA and the Clinical PET community.

2.3 Drug Formulation

Table 1. Fluorodopa F 18 Injection Drug Product Composition

COMPONENT	AMOUNT
Fluorodopa F 18	0.0155-0.3082 GBq (0.42-8.33 mCi/mL)
Acetic acid	12.72 mg
Sodium chloride	108 mg
Sterile water for injection (USP)	12 +/- 1.0 mL

The Drug Product composition is defined in the USP Monograph on Fluorodopa F18 Injection.

2.4 Comments on Novel Excipients

None.

2.5 Comments on Impurities/Degradants of Concern

No impurities or degradants of concern.

2.6 Proposed Clinical Population and Dosing Regimen

Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes. Patients are usually administered (b) (4) mg of carbidopa 60 minutes before the intravenous injection of Fluorodopa F 18 Injection at a radiologic dose of (b) (4) 5.0 mCi and a mass dose of (b) (4) mg. Positron emission tomography imaging is performed (b) (4) minutes post-injection.

2.7 Regulatory Background

NDA 200655 was first submitted by the Feinstein Institute in 2010. The Agency refused the NDA , citing inadequate clinical,nonclinical, and CMC information. The current submission is a re-submission of NDA 200655. The Division had recommended that the applicant provide Pharmacology and Toxicology information in the revised NDA, which could be accomplished by including a statement in reference to the July 28, 2000 Public Meeting between FDA CDER medical imaging staff and the Clinical PET community. The Agency's recommendation to refer to the July 2000 Public Meeting was not related to a specific safety issue; rather, to the provision of basic information in the NDA on the pharmacological basis for using the diagnostic agent, and the rationale supporting the safety of [^{18}F]FDOPA in PET imaging procedures.

Fluorodopa F18 Injection was reviewed and discussed during the July 2000 Public Meeting between FDA and the Clinical PET community. Dr. Adebayo Laniyonu presented an overview of [^{18}F]FDOPA and Levodopa pharmacology and toxicology, which was based on his review of nonclinical literature available from the public domain. The collection of references reviewed for the Public Meeting is referred to as the Agency's [^{18}F]FDOPA Master Reference List, which is attached to this review.

The outcome of the July 2000 Public Meeting discussion was that FDA deferred the decision on the approval of Fluorodopa F18 Injection to a future date. Dr. Laniyonu's Pharmacology and Toxicology Review of [^{18}F]FDOPA as a Paper NDA is attached at the end of this document.

The nonclinical section of the current NDA 200655 submission contained appropriate reference to the July 28, 2000, Public Meeting between FDA and the Clinical PET community.

It is pertinent to note that Fluorodopa F18 Injection is licensed as Dopacis® in the United Kingdom and IASOdopa in several other countries (Chevalme, Y-M, et al. 2007). The UK Summary of Product Characteristics (MHRA PL 11876-0020; 2010) describes the indication of Dopacis® " …for detecting loss of functional dopaminergic neuron terminals in the striatum in patients with clinically uncertain Parkinsonian syndromes. It

can be used to differentiate essential tremor from Parkinsonian syndromes related to degenerative diseases affecting the nigrostriatal system (Parkinson disease, multisystem atrophy and progressive supranuclear palsy)."

3 Studies Submitted

3.1 Studies Reviewed

No original nonclinical study reports were submitted by the sponsor for this 505(b)(2) New Molecular Entity NDA. The sponsor submitted summaries of 20 publically available reports on the Pharmacology and Toxicology of [^{18}F]FDOPA. The literature-based references are listed below in Table 2. The sponsor did not give reasons for the choices of articles included in the NDA.

The sponsor also made reference to a non-GLP toxicity study of [^{18}F]FDOPA in female mice, which was conducted as part of a Master's Thesis project.

Two literature reports submitted by the sponsor were reviewed in the current NDA review document. Those studies are shown in underlined, italicized font in Table 2. The remaining referenced literature reports, and additional references not included in NDA 200655, were reviewed by Dr. Adebayo Laniyonu, DMIP Pharmacologist in preparation for the July 2000 Public Meeting and were documented in a Paper NDA Review. Dr. Laniyonu's [^{18}F]FDOPA Paper NDA review is attached to this NDA review, as is the FDA [^{18}F]FDOPA Master Reference List used in the July 2000 Public Meeting.

Table 2. Nonclinical Literature Studies Submitted in Support of [^{18}F]FDOPA NDA 200655.

4.2.2.1 PRIMARY PHARMACODYNAMICS				
NDA Section	**Primary Author**	**Title of Article**	**Publication Journal Title Year Volume (no.) Page(s)**	**Cross-reference (July 2000 FDA Public Meeting Master List of References[1])**
4.2.1.1.1	Doudet, DJ	6-[18F]Fluoro-L-DOPA PET studies of the turnover of dopamine in MPTP-induced parkinsonism in monkeys	Synapse 1998 29(3) 225-32	D17
4.2.1.1.2	Firnau, G	New 18F tracers for the	Acta Radiol Suppl 1990	F6

		investigation of brain functions	374 37-41	
4.2.1.2 SECONDARY PHARMACODYNAMICS				
4.2.1.2.1	Chan, GL	Routes of administration and effect of carbidopa pretreatment on 6-[18F]fluoro-L-dopa/PET scans in non-human primates	Life Sci 1995 56(21) 1759-66	C9
4.2.1.2.2	Melega, WP	The effects of carbidopa on the metabolism of 6-[18F]fluoro-L-dopa in rats, monkeys and humans	Life Sci 1990 47(2) 149-57	M18
4.2.1.3 SAFETY PHARMACOLOGY				
4.2.1.3.1	Doudet, DJ	6-18F-L-DOPA imaging of the dopamine neostriatal system in normal and clinically normal MPTP-treated rhesus monkeys	Exp Brain Res 1989 78 69-80	D19
4.2.1.3.2	Psylla, M	Cerebral 6-{18F]fluoro-L-FDOPA uptake in rhesus monkey: pharmacological influence of aromatic amino acid decarboxylase (AAAD) and catechol-O-methyltransferase (COMT) inhibition	Brain Res 1997 767(1) 45-54	P16

4.2.1.4 Pharmacodynamic Drug Interactions				
4.2.1.4.1	*Firnau, G*	*Metabolites of 6-[18F]Fluoro-L-Dopa in human blood*	*J. Nucl. Med. 1998 29 363-69*	--
4.2.2.1 ANALYTICAL METHODS AND VALIDATION REPORTS-None submitted				
4.2.2.2 ABSORPTION				
4.2.2.2.1	Cumming, P	Metabolism of [18F] 6-Fluoro-L-3,4-Dihydroxyphenylalanine in the Hooded Rat	J. Neurochem. 1987 48(2) 601-8	Laniyonu Paper NDA, Ref. #15
4.2.2.3 DISTRIBUTION				
4.2.2.3.1	Melega, WP	Comparative in vivo metabolism of 6-[18F]fluoro-L-dopa and [3H]L-dopa in rats	Biochem Pharmacol 1990 39(12) 1843-60	M19
4.2.2.4 METABOLISM				
4.2.2.4.1	Danielson, EH	Cerebral 6-[(18)F]fluoro-L-DOPA metabolism in pig studied by positron emission tomography	Synapse 1999 33(4) 247-58	D2
4.2.2.5 EXCRETION				
4.2.2.5.1	*Khor, SP*	*The Pharmacokinetics and Pharmacodynamics of Levodopa in the Treatment of Parkinson's Disease*	*Curr. Clin. Pharmacol. 2007 2 234-43*	--
4.2.2.5.2	Brust, P	Simultaneous measurement of [18F]FDOPA metabolism and cerebral blood flow in newborn piglets	Int J Dev Neurosci 1998 16(5) 353-64	B37

4.2.2.5.3	*Bartholini, G, et al.*	*Distribution and Metabolism of L-3-O-Methyldopa in Rats*	*Brit. J. Pharmacol. 1970 40 461*	--
4.2.3 TOXICOLOGY				
4.2.3.1	*Ernst, WE*	*The Chemical Synthesis, Pharmaceutical Preparation and Toxicity analysis of Fluorodopa for Positron Emission Tomography (PET) Brain Imaging in South Africa*	*Masters Thesis, 2008, Department of Pharmacology, The University of Pretoria, SA.*	--

3.2 Studies Not Reviewed

Literature-based reports that were reviewed in 2000 by Dr. Laniyonu for the [^{18}F]FDOPA Paper NDA were not reviewed again.

3.3 Previous Reviews Referenced

Pharmacology and Toxicology Memos for IND 78861 and NDA 200655.
Paper NDA for [^{18}F]FDOPA.

4 Pharmacology

4.1 Primary Pharmacology

The sponsor described the primary pharmacology of Fluorodopa F 18 Injection in the proposed labeling (12 CLINICAL PHARMACOLOGY, 12.1 *Mechanism of Action*), which states:

(b) (4)



Reviewer's comment: The statement is the sponsor's summary of the pharmacology and mechanism of action of [^{18}F]FDOPA. The sponsor's statement was somewhat consistent with the known mechanism of action of [^{18}F]FDOPA. For additional clarifying information, the reader is referred to Dr. Adebayo Laniyonu's [^{18}F]FDOPA Paper NDA Review (July 2000), which is attached at the end of this document.

4.2 Secondary Pharmacology

No information submitted.

4.3 Safety Pharmacology

No studies submitted or required, based on the historical use of Levodopa in PD patients.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Brief Summary:
Two articles from the biomedical literature were reviewed (below). The main points of the articles were consistent with the comprehensive review of [^{18}F]FDOPA and Levodopa literature previously conducted by FDA.

NDA Section	Primary Author	Title of Article	Journal Title; Year; Volume (no.); Page(s)
4.2.2.5.1	*Khor, S-P*	*The Pharmacokinetics And Pharmacodynamics Of Levodopa In The Treatment Of Parkinson's Disease*	*Curr. Clin. Pharmacol.* | *2007* | *2* | *234-43*

Key findings:
The article is a review of the pharmacokinetics and pharmacodynamics of Levodopa and carbidopa. The authors examined and summarized various factors that influence optimal therapeutic effects of Levodopa in PD patients, with a focus on ADME profiles of long- versus short-acting formulations of Levodopa and carbidopa. The authors averred that the main means of transport of 3-O-methyldopa and Levodopa into brain is via the saturable "large neutral amino acid transport" system. The transport system is rate limiting for entry of Levodopa and 3-O-methyldopa into the brain.

Reviewer comment: The same is probably true for Fluorodopa and 3-O-methyl-6-fluorodopa, although the authors make no mention of Fluorodopa.

NDA Section	Primary Author	Title of Article	Journal Title; Year; Volume (no.); Page(s)
4.2.2.5.3	*Bartholini, G*	*Distribution And Metabolism Of L-3-O-Methyldopa In Rats*	*Brit. J. Pharmacol.* | *1970* | *40* | *461*

Key findings:
The authors concluded that L-3-O-methyldopa was present uniformly in blood plasma, brain and heart after intra-peritoneal injection in male Wistar rats. The half-life of L-3-O-methyldopa is longer than that of Levodopa (12-13 h compared with about 0.5 h).

Reviewer's comment:
The findings in the article are consistent with previously reviewed information on Levodopa.

5.2 Toxicokinetics

No information submitted or required.

6 General Toxicology

6.1 Single-Dose Toxicity

NDA Section	Primary Author	Title of Article	*Source*
4.2.3.1	*Hochfeld, W*	*The Chemical Synthesis, Pharmaceutical Preparation And Toxicity Analysis Of Fluorodopa For Positron Emission Tomography (PET) Brain Imaging In South Africa*	*Masters Thesis, Department Of Pharmacology, The University Of Pretoria, SA, 2008.*

Key Study Findings: The reference is part of a Master's Thesis document. The author conducted a non-GLP acute toxicity study of Fluorodopa F 18 injection in female mice at the University of Pretoria Department of Pharmacology. Intravenous injection of 218 µg/Kg Fluorodopa F 18 in normal saline did not produce any treatment-related effects during the 7-day post-dose observation period. The NOAEL for [^{18}F]FDOPA was (b) (4)-times the maximum human dose of (b) (4) mg per 60-Kg person (b) (4) µg/Kg), based on body weight.

Study design
Two groups of healthy, BALB/c female mice were administered an intravenous injection of 50 µL sodium chloride (0.9% w/v) (Group 1) or 218.18 µg (1 µmol) per Kg of Fluorodopa F 18 (suspended in sodium chloride (0.9% w/v) per Kg body weight.

Animals were observed for clinical signs during the 4-hour period post-injection, and twice daily thereafter for 7 days. Changes in normal activity were recorded and weights were monitored. On day 7, blood samples were collected via cardiac puncture for serum chemistry tests (AST, ALT, Albumin, Gamma-glutamyl transaminase, lactate dehydrogenase) and hematology tests (CBC with differential). Specimens of major tissues (brain, heart, kidneys, liver, spleen, pancreas, stomach, thymus, intestine (small), intestine (large) gonad, lung) were collected, weighed (brain, heart, kidneys, liver, spleen), and processed for microscopic evaluation.

Results
No signs of toxicity were observed. Both groups of animals appeared healthy throughout the 7-day period.

Food and water intake was similar in both groups.

There were no significant differences in body weights of Group 1 versus Group 2 animals.

There were no test article dependent changes in any serum chemistry or hematology tests.

There were no notable microscopic findings.

The author concluded there were no adverse findings in female mice seven days after intravenous administration of (b) (4) µg/Kg ((b) (4)µmol/Kg) Fluorodopa F 18.

Reviewer's comments:
The study is supportive of the safety of [^{18}F]FDOPA in general, with the caveat that it was conducted in a University Laboratory as part of a Master's Thesis project. There were many aspects of the study design that didn't meet typical requirements for a toxicity study in a regulatory submission (including but not limited to females only, limited evaluations, only one scheduled termination 7 days post-single dose). The study cannot be considered adequately controlled and was not conducted under any GLP guidelines. However, the study results were consistent with the known clinical safety profile of [^{18}F]FDOPA and Levodopa. The NOAEL of (b) (4) µg [^{18}F]FDOPA per Kg body weight is (b) (4)-times the maximum human dose, based on a maximum clinical mass dose of (b) (4) mg [^{18}F]FDOPA in a 60-kg person (or (b) (4)µg/Kg).

6.2 Repeat-Dose Toxicity

None submitted.

7 Genetic Toxicology

No studies submitted. The radioactive Fluorine 18 atom is considered inherently genotoxic. The Product Label should state so.

8 Carcinogenicity

Not required.

9 Reproductive and Developmental Toxicology

None submitted

10 Special Toxicology Studies

None.

11 Integrated Summary and Safety Evaluation

Fluorodopa F 18 Injection is a metabolic tracer for dopaminergic activity, based on the biochemistry and physiology of striatal function. The receptor biology and biochemical transformations of Fluorodopa F 18 Injection that occur in striatal neurons form the basis of the mechanism of action of [^{18}F]FDOPA in the brain.

Prior to the submission of NDA 200655, typical pharmacology and toxicology studies required for an NDA application were waived, based on the Agency's review of the

publicly available nonclinical information, which was conducted by Dr. Adebayo Laniyonu (1). The available information was found to be acceptable in lieu of conventional Pharmacology and Toxicology studies for Fluorodopa F 18 Injection based on the following factors:

1) Clinical experience with Fluorodopa F 18 Injection, without reports of safety concerns;
2) Comprehensive Levodopa historical database and 30+ years experience in chronic clinical use at daily doses more than 1000-fold the one-time [^{18}F]FDOPA dose of (b) (4) mg;
3) Similarity in the metabolism and disposition of Levodopa and [^{18}F]FDOPA; and
4) Low mass dose of [^{18}F]FDOPA administered in PET studies.

Two literature-based reports and a non-GLP toxicity study were reviewed in this document. The information in the reports provided additional, albeit minimal, evidence that Fluorodopa F 18 Injection is safe for the maximum recommended intravenous mass dose of (b) (4) mg and radiologic dose of 5 mCi.

Based on the factors listed above, I recommend that NDA 200655 may be approved from the Pharmacology and Toxicology perspectives.

12 Attachments

1. Laniyonu, Adebayo. *Paper NDA Pharmacology and Toxicology Review of [^{18}F]FDOPA.* Internal CDER, OND, DMIP Report; July 2000.

2. [^{18}F]FDOPA Master Reference List.

References

[^{18}F]FDOPA Master Reference List; available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm182855.htm

Transcript of the July 28, 2000 Public Meeting; available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm182855.htm

Medicines and Health Care Regulatory Agency (MHRA), United Kingdom, PL 11876-0020; 2010.

Chevalme, Y-M, et al. Brazilian Archives of Biology and Technology, Vol.50, Special Number : pp.77-90, September 2007.

Carbidopa/Levodopa Monograph 2013, Drug Facts and Comparisons® eAnswers, accessed on 05/30/2013 via the FDA Library.

ATTACHMENT 1

Laniyonu, Adebayo. *Paper NDA Pharmacology and Toxicology Review of [^{18}F]FDOPA.* Internal CDER, OND, DMIP Report; July 2000.

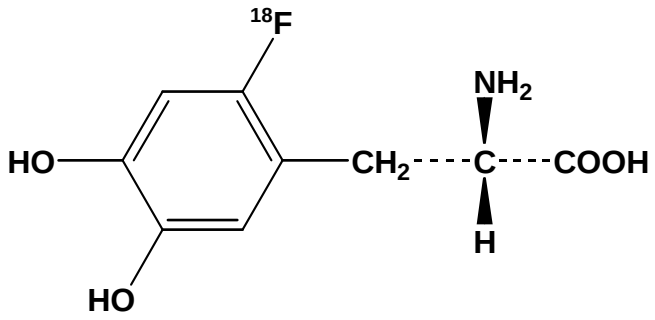
Review and Evaluation of Pharmacology and Toxicology Data

Division of Medical Imaging and Radiopharmaceutical Drug Products
HFD-160
Reviewer: Adebayo, A. Laniyonu, Ph.D.

Chemical Name: 3-(2-Fluoro-^{18}F-4,5-dihydroxy-phenyl)-L-alanine

CAS Number: 92812-82-3

Structure:



Molecular Weight: 214.18

Relevant NDA: N-19-856, N-17-555

Drug Class: Positron Emission Tomography (PET) Radiopharmaceutical

Indication: (b) (4)

Clinical Formulation (and components):

Route of Administration: Intravenous

Introduction/Drug History:

There are published articles concerning the clinical utility of [^{18}F]Fluorodopa in evaluation of alterations in presynaptic dopaminergic system especially as it relates to neurology [1,2,3,4,5,6]. However, the agency has not granted approval for any indication. PET radiopharmacueticals are usually manufactured close to the site of use due to the relatively short half-life of these products. Unlike a conventional application, this review is not evaluating a known formulation, hence different production pathway may impact on the purity and toxicological profile of [^{18}F]Fluorodopa since different PET centers are responsible for production. A major purpose of this survey is to review the available scientific literature in an attempt to examine the scientific basis of use and, to determine whether Pharmacology/Toxicology studies typically conducted and

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considered critical to support the safety of an NDA application have been reported in the literature. This is not a typical NDA review, because the experiments upon which the scientific evidence are based were not conducted with an NDA format in mind. Nevertheless, all the articles were published in peer reviewed journals and the most of the findings were reported from multiple laboratories. This review aims to (1) identify the concepts that are scientifically valid and that appear to have general support within the scientific community and (2) Identify the areas where more information is required.

Previous clinical experience:

[^{18}F]Fluorodopa has been utilized in the evaluation of alterations in presynaptic dopaminergic system especially as it relates to neurological needs from multiple clinical centers. No adverse reaction to the radiopharmaceutical has been documented at clinically relevant doses. (see medical officer review).

Pharmacology:

An understanding of the conceptual basis for the use, and limitation of [^{18}F]Fluorodopa in the evaluation of alterations in presynaptic dopaminergic system requires a brief overview of 1), The biosynthesis and metabolism of dopamine and [^{18}F]Fluorodopamine, 2), similarities and differences in the way the body handles F-DOPA and L-DOPA, and, 3) integration of how [^{18}F]Fluorodopa fits into the contextual evaluation of alterations in presynaptic dopaminergic system.

Biosynthesis and metabolism of Dopamine:

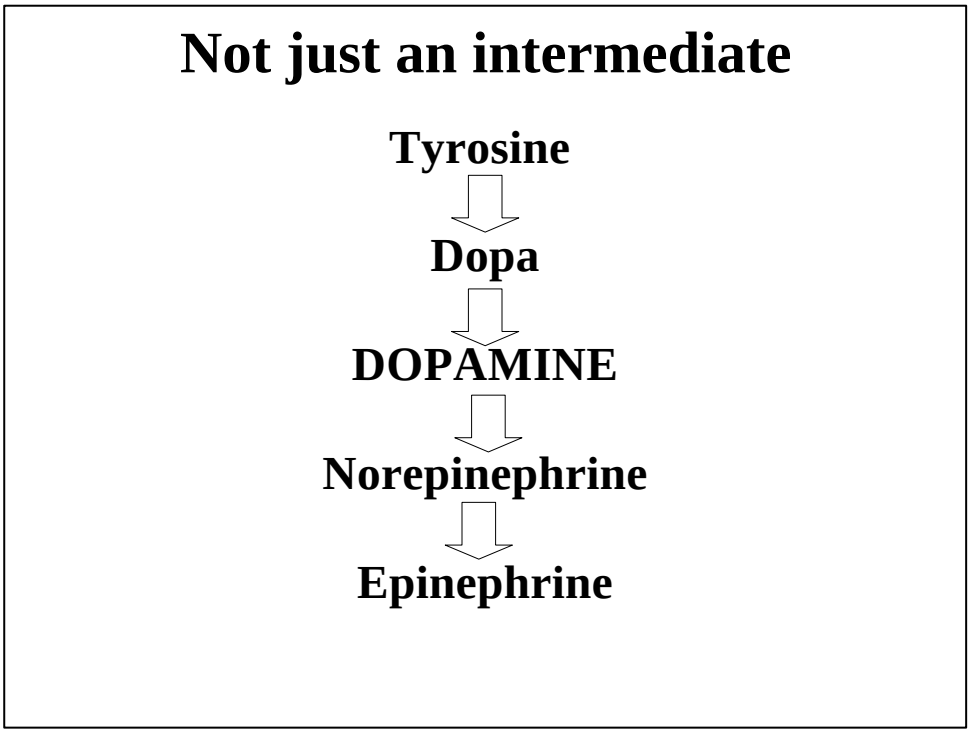


Fig 1: Schema for the synthesis of norepinephrine and epinephrine

Once considered solely an intermediate in the biosynthesis of the catecholamines, the role of dopamine as a neurotransmitter in its own right is now firmly established [7]. The early impetus

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for such consideration came largely from Scandinavian investigators [7,8]. They demonstrated distribution of dopamine in peripheral organs, and provided evidence of brain dopamine concentration in greater amount than would have been anticipated solely from a precursor role. More importantly, there were marked differences in regional distribution of dopamine, and the sympathomimetic neurotransmitter, norepinephrine both within the central nervous system and in bovine peripheral tissues.

The synthesis of dopamine occurs in the terminals of dopaminergic neurons [4,7,8]. Dopamine does not cross the blood brain barrier from the systemic circulation. However, the synthetic precursor, tyrosine is transported across the blood brain barrier through an active transport process. Within the neuronal terminals, it is converted to dihydroxyphenylalanine (L-DOPA) by the enzyme, tyrosine hydroxylase (TH). This conversion represents the rate-limiting step in the biosynthesis of dopamine. L-DOPA is converted rapidly to dopamine by aromatic L-amino acid decarboxylase (AAAD). In the terminal, dopamine is taken up into the storage vesicle by a transporter protein associated with the vesicular membrane where its release is triggered by depolarization and entry of calcium. The released dopamine acts on postsynaptic dopamine receptors. It is noted that L-DOPA can be acted upon by peripheral COMT to produce 3-O methyldopa, which is able to cross the blood brain barrier.

Dopamine effects are terminated by the enzymes monoamine oxidase (MAO) and cathecol-O-methyl-transferase (COMT) to yield two metabolic products, 3, 4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxy-4-dihydroxyphenylacetic acid (HVA). Dopamine transporter (DAT) located on the presynaptic nerve terminal is involved in terminating dopaminergic transmission by transporting dopamine back into the dopaminergic neuron for storage. DAT has also been suggested to be a possible marker of the integrity of the dopaminergic nerve terminal [7].

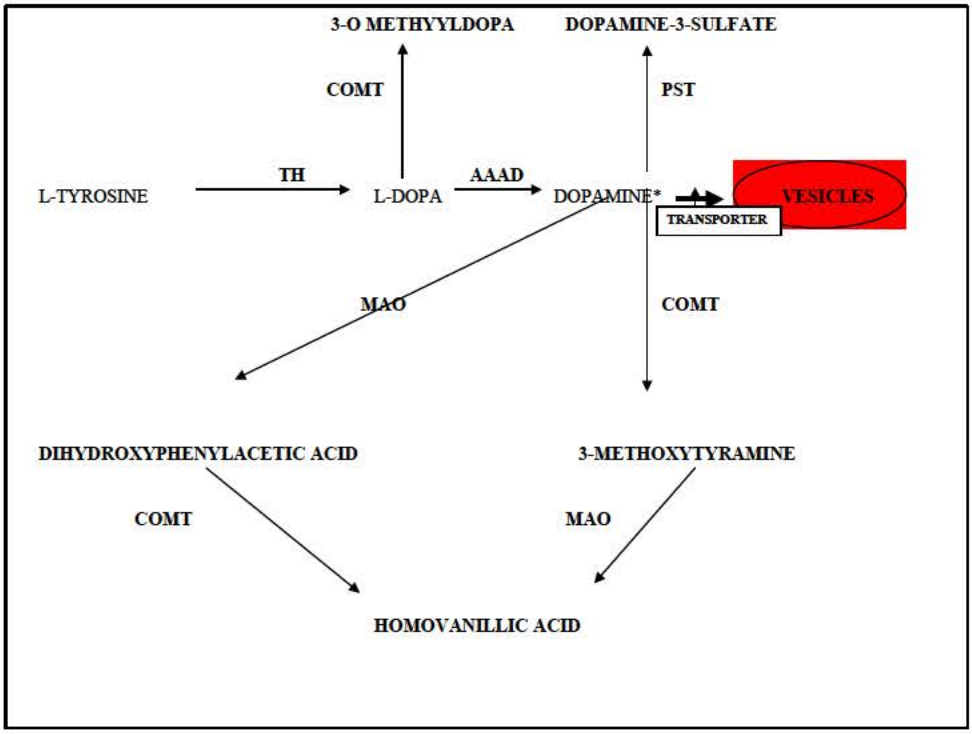


Fig 2: Schema for the synthesis of Dopamine

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The metabolism of [^{18}F]Fluorodopa (FD) is handled in a similar manner to that of L-DOPA. The uptake and trapping of ^{18}F radioactivity into the striatum after intravenous injection of [^{18}F]Fluorodopa requires the following: (1) a working transporter for FD through the blood-brain barrier, (2), adequate residue of AAAD activity, and (3) a functioning vesicular storage apparatus for fluorodopamine in the region [1,9] In the basal ganglia, [^{18}F]Fluorodopa is converted to [^{18}F]Fluorodopamine (FDA) by AAAD. Thereafter, it is taken up into the storage vesicle where it can be released like dopamine. FDA is acted upon by MAO and COMT to yield 6-[^{18}F]Fluoro-3,4-dihydroxyphenylacetic acid (FDOPAC), and [6-[^{18}F]Fluorohomovanillic acid (FHVA). In the systemic circulation, [^{18}F]Fluorodopa is also acted upon by COMT to produce 3-O-methyl[^{18}F]dopa (3-O-MFDOPA) or decarboxylated by peripheral AAAD to fluorodopamine (FDA). 3-OMFDOPA can cross the blood brain barrier more rapidly than FD.

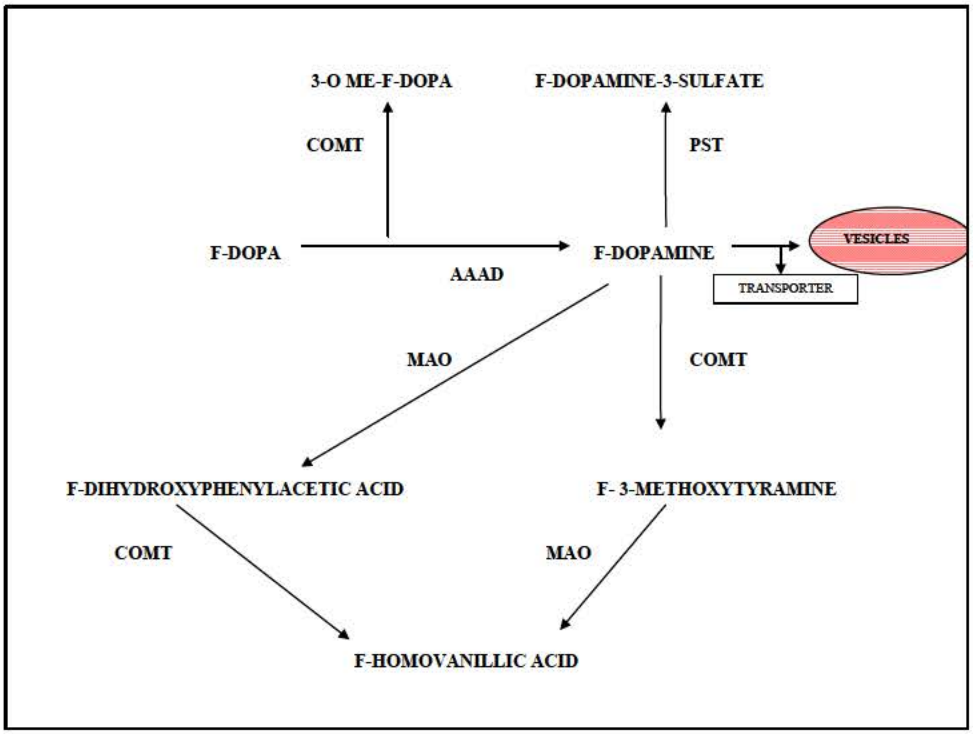


Fig3:Schema for the synthesis of fluorodopamine

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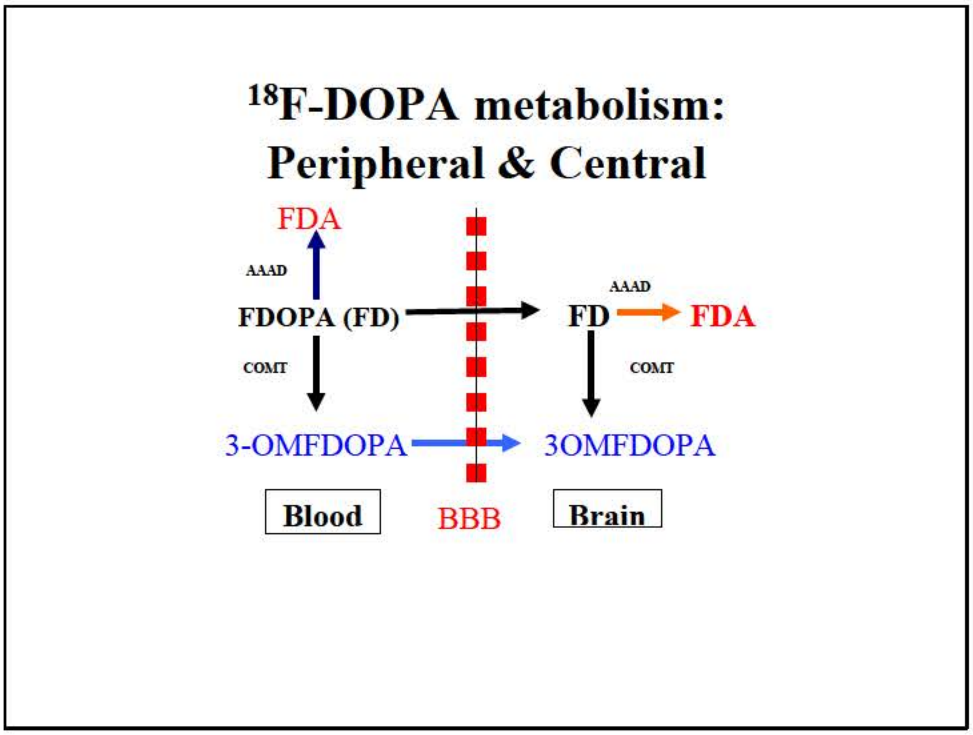


Fig4: [18]F-Dopa metabolism: peripheral and central

In addition to its accumulation within the dopaminergic neurons, it is theoretically possible for FDA to accumulate within the adrenergic nerve terminals since FDA can be converted be to [^{18}F]-labeled norepinephrine by the enzyme dopamine hydroxylase.

Influence of enzyme inhibitors on handling of FDOPA:

The two principal enzymes influencing the metabolism of FDOPA are aromatic amino acid decarboxylase (AAAD) and catechol-O-methyltransferase (COMT). Both enzymes are present peripherally and centrally. In the absence of enzyme inhibitors, intravenously administered FDOPA is subject to metabolism by these enzymes. Decarboxylation by AAAD leads to formation of fluorodopamine. O-methylation by COMT results in the formation of 3-OMFDOPA. The net result of peripheral metabolism is to reduce the amount of FDOPA available to cross the blood brain barrier. In addition, peripherally formed FDA has physiological actions similar to Dopamine. These actions result from stimulation of both adrenergic and dopaminergic receptors. Unlike FDA, 3-OMFDOPA penetrates the blood brain barrier.

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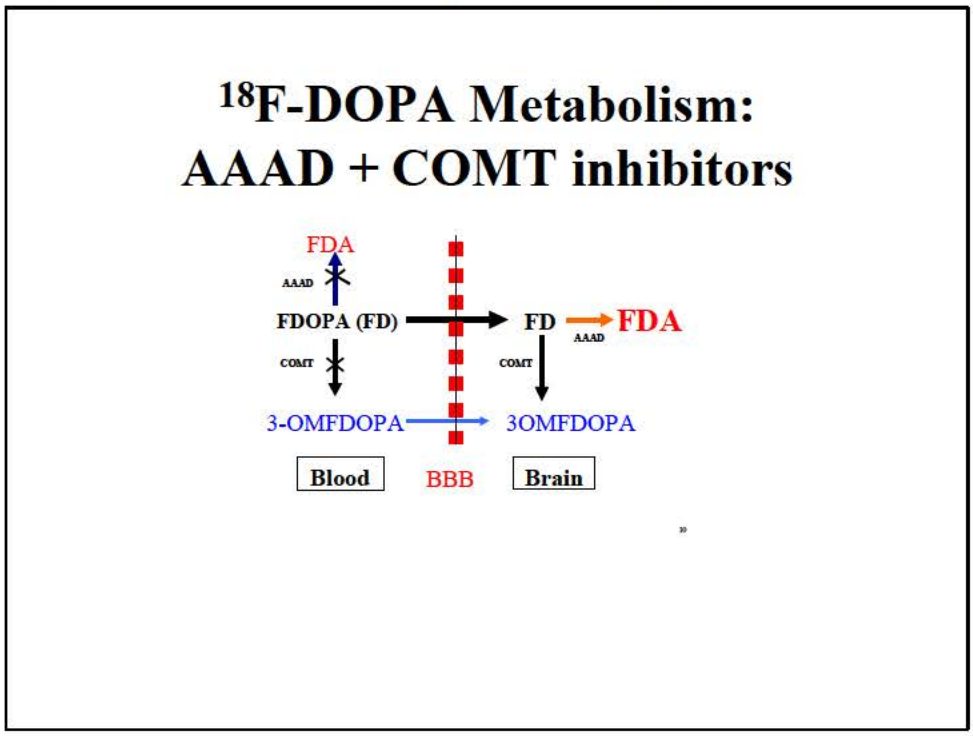


Fig5: ^{18}F-Dopa metabolism: Influence of AAAD and COMT inhibitors

In the presence of both AAAD and COMT inhibitors, peripheral metabolism of FDOPA is inhibited, and intravenously administered FDOPA is able to enter the CNS almost in its entirety.

Pharmacokinetics:

The major pathways in the peripheral and central metabolism of FDOPA have been discussed under biosynthesis and metabolism. In the absence of a decarboxylase inhibitor, the major peripheral metabolites detected in plasma were 3-OMFDOPA, FDA and, its conjugated metabolites. Carbidopa pretreatment prevents decarboxylation to FDA, increasing FDOPA bioavailability, however, FDOPA can still be metabolized by COMT to 3-OMFDOPA [10, 11, 12, 13].

The plasma level of FDOPA declines rapidly following intravenous injection [13]. The major metabolite appearing within the first 60 minutes following injection is 3-OMFDOPA. Carbidopa increases both the plasma level and the plasma $t_{1/2}$ of FDOPA [11].

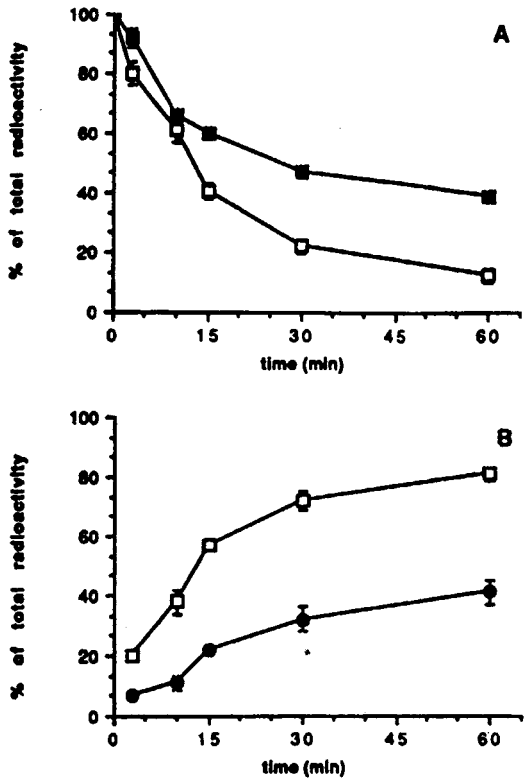


Fig: 6: (A) Clearance of [18F]FDOPA (□)and [3H]L-DOPA (■) from plasma (B) Plasma level of [18F]OMFDOPA (□) and [3H]3-OMDOPA (·) after double-label injection of [18F]FDOPA and [3H]L-DOPA. Animals were pretreated with carbidopa (5mg/kg. s.c.) 60 minutes before injection of [18F]FDOPA (800 uCi/kg (0.4-0.8 umol/kg, iv) and [3H]DOPA (150uCi/kg (3.8nmol/kg, i.v. n=6) (Melega W.P. et.al. 1990, Biochemical Pharmacology 12, 1853-1860

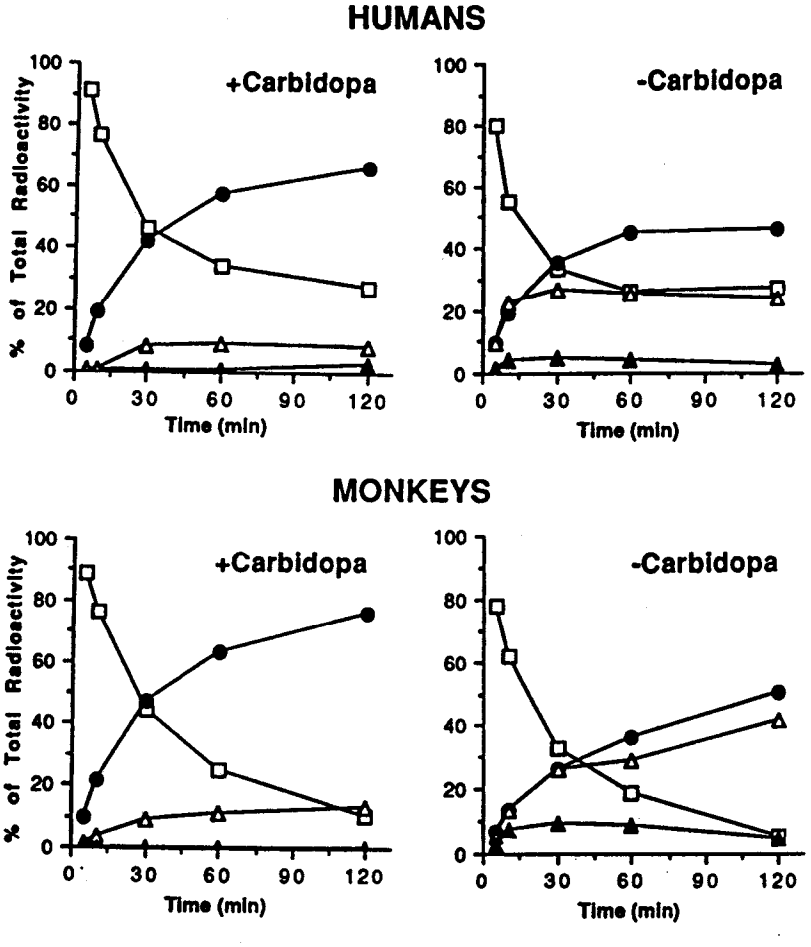


Fig 7: Effect of carbidopa on percent ^{18}F-radioactivity plasma profiles for humans (n=5) and for monkeys (n=5) (Melega, W.P. et.al. 1990, Life Sciences, 47 149-157)

Both FDA and 3-OMFDOPA are the principal metabolites formed within the CNS (see discussion below).

Relative importance of 3-o-methylfluorodopa on imaging acquisition:

3-O-methylfluorodopa is formed from intravenously administered FDOPA in the absence of a peripheral COMT inhibitor. This metabolite is capable of crossing the blood brain barrier. The question then arises as to whether 3-OMFDOPA affects imaging in terms of contributing to non-specific background signal. Two schools of thought emerged from the review of the literature.
The first, and to a large extent the majority opinion, suggests that non-specific imaging interference by 3-OMFDOPA is significant, and that the rate and extent of 3-OM-methylation of [18F]DOPA exceed that of [^{3}H]DOPA or [^{11}C]DOPA [10-15].

In a study examining FDOPA metabolism in monkeys, Barrio and his workers [10] examined the relative importance of 3-OMFDOPA to the metabolite profile of FDOPA following peripheral inhibition of AAAD enzyme. The animals were administered carbidopa (5mg/kg, i.v.) prior to administration of FDOPA, (5-8 mCi, i.v., specific activity 1-2 Ci/mmol). Plasma and brain

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samples were taken for quantification of ^{18}F metabolites. The results indicated that 3-OMFD was the major metabolite detected in all regions of the brain examined (putamen, caudate, frontal cortex and cerebellum). FDA was detected only in caudate and putamen. Other metabolites detected in both regions include FDOPAC, and FHVA.

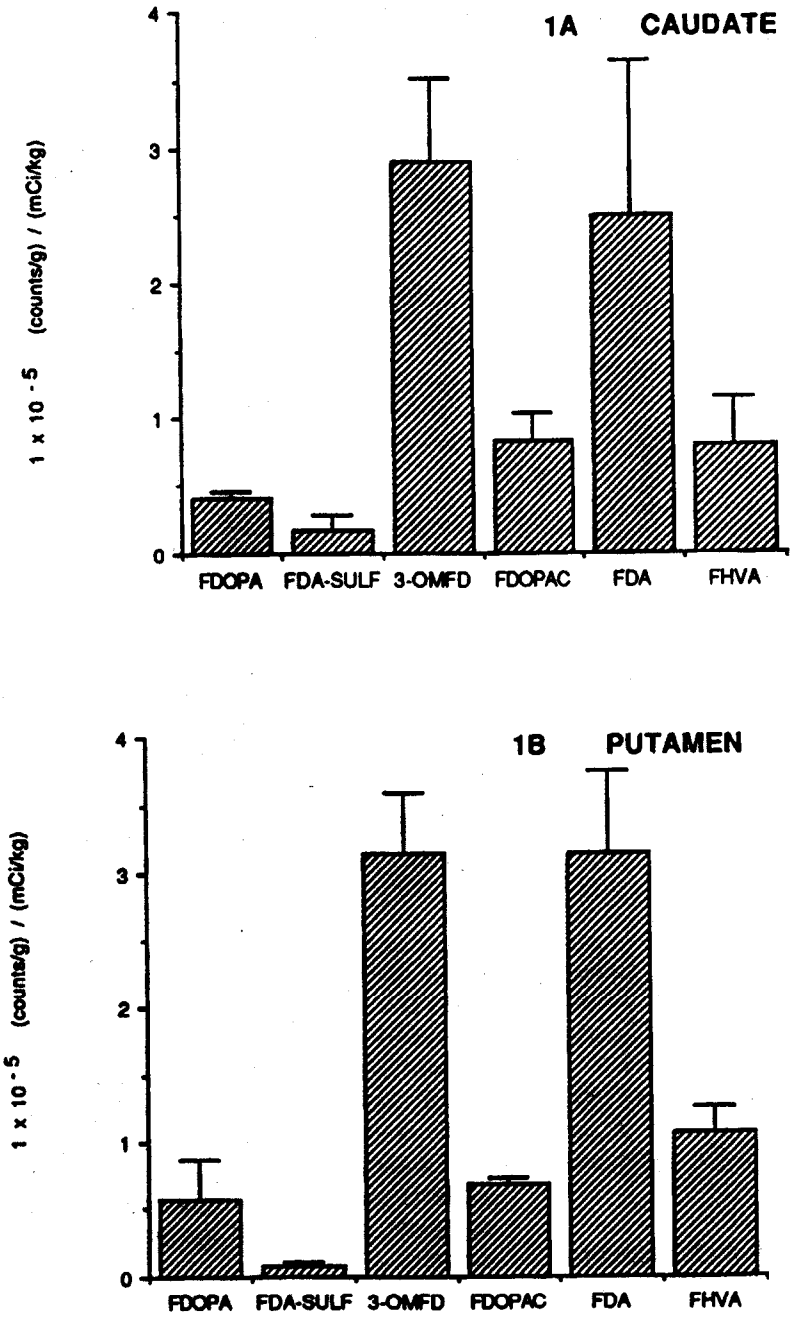


Fig 8: Distribution of FDOPA metabolites in monkey caudate (A) and putamen (B) at 60 minutes (mean SD , n=3. FDA represented 33% of the total activityin the caudate and 35%in the putamen; 3-OMFD = (3-OMFDOPA) accounted for 38% and 35% respectively (Melega, W.P. et.al. 1991, J of cerebral blood flow and metabolism, 11, 890-896)

Reference ID: 3322236

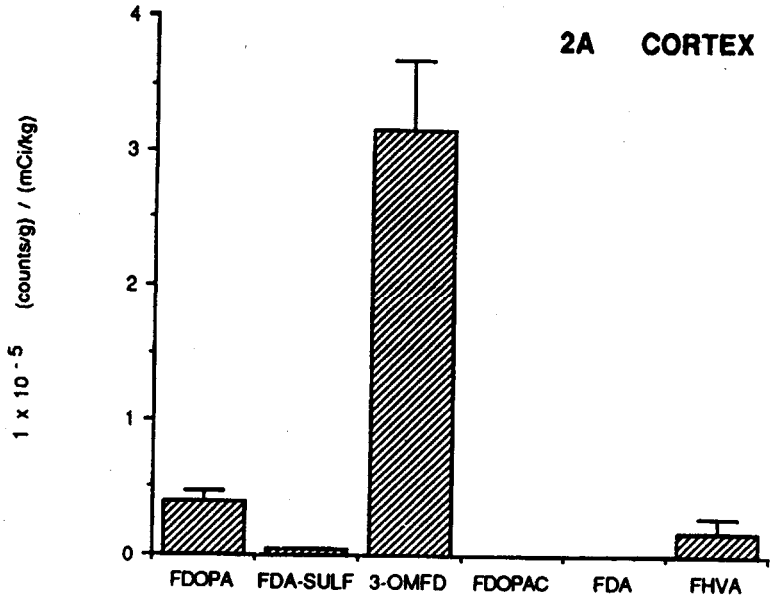


Fig 9: Distribution og FDOPA metabolites in monkey cortex at 60 minutes (mean, DS , n=3). 3-OMFD = 3-OMFDOPA) accounted for 80% of the total activity (Melega, W.P. et.al. 1991, J of cerebral blood flow and metabolism, 11, 890-896)

The plasma FDOPA metabolites profile at 60 minutes consisted primarily of FDOPA, 3-OMFDOPA, FDA sulfate with 3-OMFDOPA being the predominant metabolite.

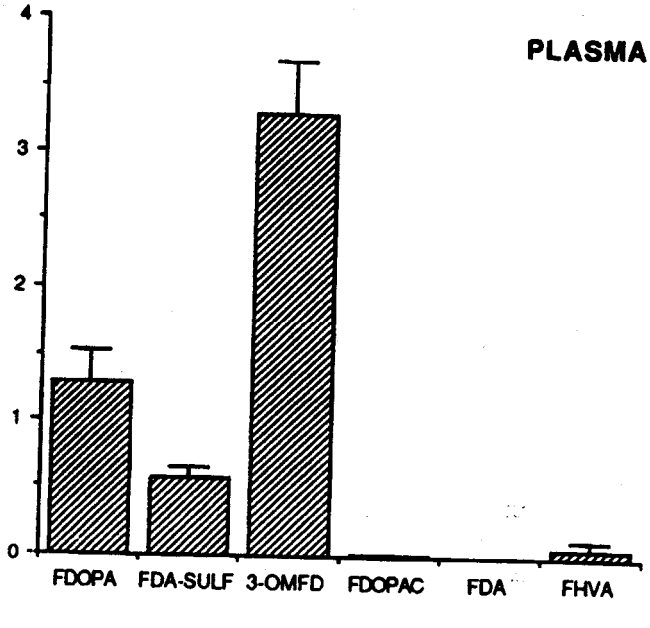


Fig 10: Distribution of FDOPA metabolites in monkey plasma at 60 min (mean SD, n=3). 3-OMFD accounted for 70% of the total activity. FDA formation was detected only as the sulfate.

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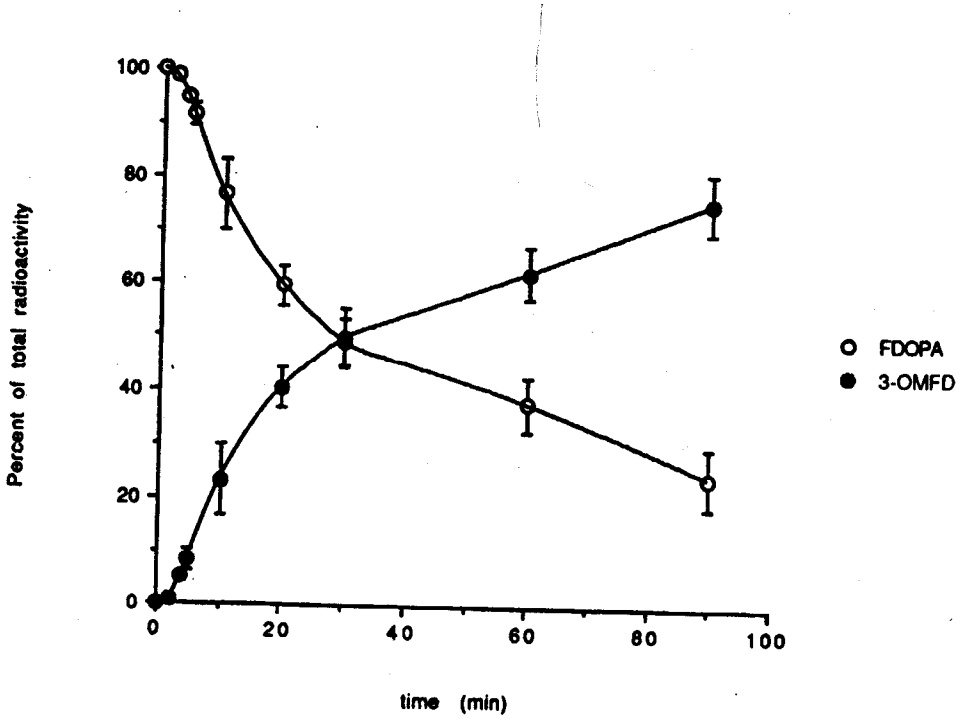


Fig 11: Percentage of total radioactivity versus time for FDOPA and 3-OMFD in human plasma (mean SD, n =6) other FDOPA metabolites were not detected (Melega, W.P. et.al. 1991, J of cerebral blood flow and metabolism, 11, 890-896)

In a human study carried out by the same group [10], male human volunteers were fasted for at least 6 hours, then administered carbidopa, (200 mg p.o). FDOPA (4-8 mCi , i.v.) was given 90 minutes later. Arterial blood samples were collected at intervals. The results suggested that plasma metabolism was restricted to 3-OMFD formation.

Many laboratories have examined the influence of COMT inhibition of FD metabolism [16, 17, 18, 19]. Ruottinen et.al. [19] studied striatal fluorodopa utilization after COMT inhibition with entacapone in healthy humans and in advanced parkinsonian patients. Entacapone significantly enhanced the fraction of unmetabolized FDOPA in plasma and thus its availability in the brain for decarboxylation both in patients and control subjects.

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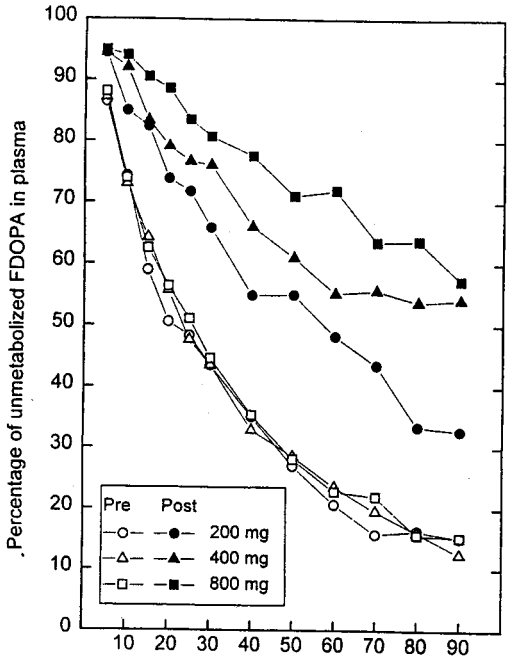


Fig:12 The effect of various doses of entacapone on FDOPA fraction in the arterial plasma of PD patients, expressed as a mean percentage of unmetabolized FDOPA calculated from the sum of HPLC fractions of FDOPA and its metabolites. Pre without entacapone, post with entacapone (Ruottinen, H. M. et.al. 1995, J Neural Transm 10, 91-106)

The implication of a significant distribution of 3-OMFD throughout the brain from contribution of 3-O-methyl[^{18}F]dopa entering from the periphery in the absence of COMT inhibition is that it contributes to the background activity in PET images thus decreasing the contrast between striatal and reference regions. In analysis employing total radioactivity count, the contributive effect of this metabolite to both background and striatal uptake will complicate the interpretation of images obtained. It is therefore necessary to distinguish the signal in cerebral tissues due to the entrapment of locally decarboxylated compounds especially since 3-OMFDOPA crosses the blood brain barrier more readily than F-DOPA. Alternatively, this interference would make concomitant administration of a COMT inhibitor during FDOPA-PET a necessity.

The second school of thought emanating mainly from the laboratory of Firnau and co-workers believes that non-specific interference by 3-OMFDOPA is minimal, and that FDA is the major metabolite formed following the administration of FDOPA.

Firnau and colleagues [20, 21] evaluated the cerebral metabolism profile of FDOPA in rhesus monkeys fasted for twelve hours prior to study commencement. The animals received FDOPA (1.8-5.3 mCi, i.v.). It is pertinent to note that AAAD inhibitor was not used to block the peripheral decarboxylation of FDOPA to FDA. Arterial samples were obtained, and at specific time intervals, animals were euthanized to obtain cerebral tissue samples. The results of the study suggested that FDA was the major striatal metabolite produced, accounting for about 70% of total metabolites at 30 minutes, and for about 50% at 70 minutes. Similar metabolite profile was also obtained in a study conducted on healthy human volunteers that were given FDOPA, 4-6 mCi, I.V.).

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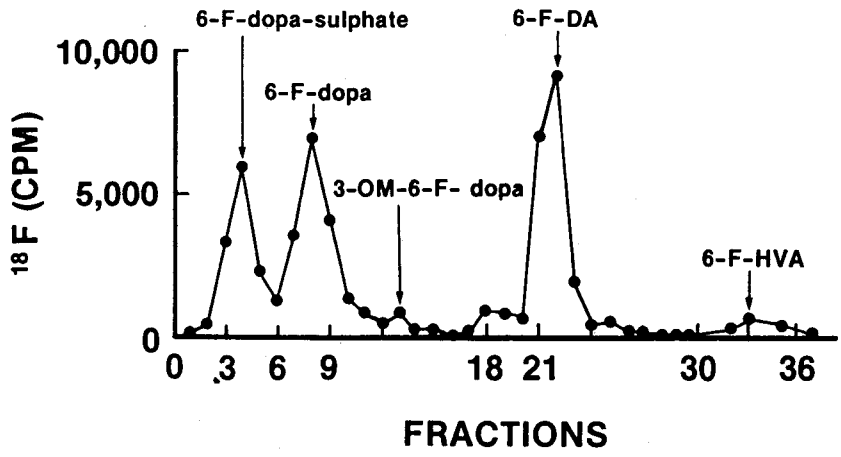


Fig 13: Liquid chromatogramme of the extract of human plasma taken 30 minutes after injection of ^{18}[F]fluoro-L-dopa (Firnau, G. et.al. 1988, J Nucl Med 29: 363-369).

The authors accounted for the results in terms of substrate specificity. Specifically, they argued that in the periphery, FDOPA was less reactive than LDOPA as a substrate for O-methylation and that consequently only FDOPA was available for brain uptake and metabolism to Fluorodopamine. Therefore, one can assume that in studies of cerebral dopamine metabolism involving FDOPA and PET, that the time-activity curve of FDOPA in arterial sample represent the input function of the brain since minimal amount of 3-OMFD is produced peripherally. None specific background contribution from 3-OMFD is minimal. It bears emphasizing that Firnau's laboratory was the only laboratory that reached this conclusion. The preponderance of evidence in the literature suggested that 3-O-methyl[^{18}F]dopa entering from the periphery in the absence of COMT inhibition contributes to the background activity in PET images thus decreasing the contrast between striatal and reference regions.

My considered opinion is that I agree with the school of thought suggesting that non-specific interference is significant, and should be accounted for image acquisition technique or in image analysis

Use of [^{18}F]Fluorodopa in evaluation of alterations in presynaptic dopaminergic system

From a mechanistic perspective, the intuitive appeal of [^{18}F]Fluorodopa as a marker of the integrity of the dopaminergic system is obvious; there is a correlation between the accumulation of ^{18}F activity and the functional integrity of the dopaminergic neurons, and the activity is attributable to AAAD-mediated formation of FDA [1, 2, 3, 4]. Moreover, preclinical image acquisition studies (PET) have been conducted in primates administered N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [22-26]. Such primates have served as a model of parkinsonism. Intravenous administration of MPTP produces a disorder like parkinsonism (akinesia, rigidity, postural tremor, flexed posture, eyelid closure and tremor [23-24]). Biochemical correlates include severe nerve cell loss in substantia nigra, and a marked reduction in the dopamine content of the striatum. In PET studies, ^{18}F accumulation was significantly reduced in the stiatum, putamen of the MPTP-treated animals compared to the normal controls. ^{18}F accumulation in the cortex did not differ between control and MPTP-treated animals. The

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results suggest that vesicular striatal FDA uptake in PET studies is a good index of striatal dopaminergic function. However, as succinctly summarized by Barrio and his colleagues [1], several questions remain largely unanswered as regard the underpinning mechanistic assumptions. For example, 1), how closely does exogenous FDOPA uptake represent endogenous dopamine synthesis given the fact that FDOPA metabolism by AAAD bypasses the influence of tyrosine hydoxylase which is the rate-limiting step in the endogenous dopamine synthesis. 2), Could FDOPA decarboxylation become the rate-limiting step unlike in endogenous conditions where FDOPA decarboxylation is independent of AAAD concentration. 3), is FDOPA kinetics related to other endogenous parameters such as dopaminergic cell number. For example, the sensitivity of FDOPA kinetics on AAAD may not be apparent in the early pre-symptomatic stages of nigrostriatal dopaminergic degeneration when neuronal plasticity may allow for compensatory sprouting of axonal bearing synapses leading to no significant changes in terminal numbers and AAAD concentration

Toxicology:

The literature survey did not identify any study that examined the toxicity profile of FDOPA or that quantified impurities or excipients. However, LDOPA (usually administered with a decarboxylase inhibitor) is an approved drug product with more than 30 years of clinical use in the treatment of parkinsonism and related disorders. There is extensive safety database for LDOPA. The side effects of LDOPA are largely attributed to dopamine, formed from its decarboxylation by AAAD. The side effects include nausea, confusion and hallucination, especially in the elderly and those with pre-existing cognitive dysfunction. Peripheral action of dopamine on the cardiovascular system include hypotension, cardiac arrhythmia especially in patients with pre-existing conductance disturbance [7].

These side effects LDOPA occur at much higher dose range than those anticipated for FDOPA use in PET imaging studies. Daily dose of L-DOPA is about 500-1000 mg. A 10mCi single dose of FDOPA contains approximately (b) (4) mg of the drug substance. The availability of extensive clinical experience with FDOPA without reports of safety-related concern, safety data base for LDOPA, and the fact that FDOPA will be administered in tracer quantity ameliorate the lack of toxicity data for the time being.

Carcinogenicity:

No study addressing the carcinogenicity of FDOPA was identified

Immunotoxicology:

No study addressing the immunotoxicity of FDOPA was identified

Reproductive Toxicology:

No study addressing the reproductive toxicology of FDOPA was identified

Genotoxicity

No study addressing the genotoxicity of FDOPA was identified

Reference ID: 3322236

Overall Summary:

This review has relied heavily on the similarity between L-DOPA and FDOPA metabolism, and the way both are handled by the body. That FDOPA acts as a substrate for AAAD, and has been used as a biochemical marker of the dopaminergic system is well documented. What is less clear is the detailed clinical interpretation of the results meaning. Although the number of both preclinical and clinical publications on FDOPA is impressive, results interpretation is confounded by our lack of how disease conditions, technology and methodology affect the fundamental mechanistic assumptions governing the use of FDOPA.

From a regulatory perspective, the issue of whether pharmacology/toxicology studies typically conducted and considered critical to support the safety of an NDA have been reported in the literature was examined. No study specifically addressing the toxicology, carcinogenicity, genotoxicity, reproductive toxicology or immunotoxicology of FDOPA were identified in the literature. However, extensive clinical experience without reports of safety related concerns, similarity in the metabolism of LDOPA and FDOPA, safety data base for LDOPA, together with the fact that FDOPA is administered in low mass dose, ameliorate lack of data for the time being. Therefore the need for typical pharmacology and toxicology studies can be waived.

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Reviewer's Signature:

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Team leader Concurrence:

Nakissa Sadreih, Ph.D.

Reference ID: 3322236

ATTACHMENT 2

[^{18}F]FDOPA Master Reference List.

PET: F-DOPA LITERATURES
[MASTER INDEX]

Tab #	Origin	Primary Author	Title	Journal	Year Published	Volume	Pages
A1		Abbott NJ	Delivery of imaging agents into brain	Adv Drug Deliv Rev	1999	37(1-3)	253-77
A2		Abe Y	[Diagnostic utility of positron emission tomography for parkinsonism after chronic manganese exposure.]	Rinsho Shinkeigaku	1999	39(7)	693-9
A3		Agid Y	The efficacy of levodopa treatment declines in the course of Parkinson's disease: do nondopaminergic lesions play a role?	Adv Neurol	1990	53	83-100
A4		Agid Y	Pathophysiology of L-dopa-induced abnormal involuntary movements	Psychopharmacology Suppl	1985	(64)2	93-103
A5	27 (A2)	Antonini A	Complementary PET studies of striatal neuronal function in the differential diagnosis between multiple system atrophy and Parkinson's disease	Brain	1997	120(Pt 12)	2187-95
A6		Antonini A	Long-term changes of striatal dopamine D2 receptros in patients with Parkinson's disease: a study with positron emission tomography and [11C]raclopride	Mov Disord	1997	12(1)	33-8
A7	(A1)	Antonini A	Complementary positron emission tomographic studies of the striatal dopaminergic system in Parkinson's disease	Arch Neurol	1995	52(12)	1183-90
A8		Antonini A	[11C]raclopride and positron emission tomography in previously untreated patients with Parkinson's disease: Influence of L-dopa and lisuride therapy on striatal dopamine D2-receptors	Neurology	1994	44(7)	1325-9
A9	[A9]	Aquilonius SM	What has PET told us about Parkinson's disease?	Acta Neurol Scand Suppl	1991	136	37-9

PET: F-DOPA LITERATURES
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Tab #	Origin	Primary Author	Title	Journal	Year Published	Volume	Pages
A10		Aquilonius SM	Brain dopaminergic mechanisms in Parkinson's disease evaluated by positron emission tomography	Acta Neurol Scand Suppl	1989	126	55-9
A11		Aquilonius SM	In vivo evaluation of striatal dopamine reuptake sites using 11C-nomifensine and positron emission tomography	Acta Neruol Scand	1987	76(4)	283-7
A12		Asahina M	[Muscarinic cholinergic receptor imaging of parkinsonian brain using 11C-NMPB and PET]	Nippon Rinsho	1997	55(1)	233-7
A13		Asahina M	Hypersensitibity of cortical muscarinic receptors in Parkinson's disease demonstrated by PET	Acta Neurol Scand	1995	91(6)	437-43
B1	56	Badawi RD	3D-Mode acquisition of clinical PET	Nucl Med Commun	1997	18	801-4
B2	57	Bailey DL	A convolution-subtraction scatter correction method for 3D PET	Phys Med Biol	1994	39	411-24
B3	14	Bailey DL	3D acquisition and reconstruction in positron emission tomography	Ann Nucl Med	1992	6(3)	123-30
B4	(A5) [ICP 1]	Barrio JR	Biological imaging and the molecular basis of dopaminergic diseases	Biochem Pharmacol	1997	54(3)	341-8
B5		Barrio JR	Radiofluorinated L-m-tyrosine; new in-vivo probes for central dopamine biochemistry	J Cereb Blood Flow Metab	1996	16(4)	667-78
B6	(B3) [ICP 2]	Barrio JR	6-[18F]fluoro-L-dopa probes dopamine turnover rates in central dopaminergic structures	J Neurosci Res	1990	27(4)	487-93
B7	21	Bernheimer H	Brain dopamine and the syndromes of Parkinson and Huntington	J Neurol Sci	1973	20	415-55

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B8		Bhatt MH	Positron emission tomgraphy in progressive supranuclear palsy	Arch Neurol	1991	48(4)	389-91
B9		Blesa R	[PET and SPECT in Parkinson's disease].	Rev Neurol	1997	25 Suppl 2	S147-50
B10	(A6)	Boecker H	Secondary parkinsonism due to focal substantia nigra lesions: a PET study with [18F]FDG and [18F]fluorodopa	Acta Neurol Scand	1996	93(6)	387-92
B11		Bohnen NI	(+)-alpha-[11C]Dihydorteteabenazine PET imaging in familial paroxysmal dystonic choreaoathetosis	Neurology	1999	52(5)	1067-9
B12		Booij J	Practical benefit of [123I]FP-CIT SPET in the demonstration of the dopaminergic deficit in Parkinson's disease	Eur J Nucl Med	1997	24(1)	68-71
B13	(A7) [ICP 3]	Boyes BE	Determination of plasma [18F]-6-fluorodopa during positron emission tomography: elimination and metabolism in carbidopa treated subjects	Life Sci	1986	39(23)	2243-52
B14		Brannan T	In vivo studies of striatal dopamine release and metabolism following administration of L-dopa	Adv Neurol	1990	53	75-81
B15		Brashear A	PET imaging of the pre-synaptic dopamine uptake sites in rapid-onset dystonia-parkinsonism (RDP)	Mov Disord	1999	14(1)	132-7
B16	67	Brooks DJ	The early diagnosis of Parkinson's disease	Ann Neurol	1998	44 (3sup1)	S10-8
B17	[B17]	Brooks DJ	Positron emission tomography studies in movement disorders	Neurosurg Clin North Am	1998	9(2)	263-81
B18		Brooks DJ	Motor disturbance and brain functional	Eur Neurol	1997	38	26-32

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			imaging in Parkinson's disease			Suppl 2	
B19	24	Brooks DJ	Advances in imaging Parkinson's disease	Curr Opin Neurol	1997	10(4)	327-31
B20		Brooks DJ	PET and SPECT studies in Parkinson's disease	Baillieres Clin Neurol	1997	6(1)	69-87
B21	[B21]	Brooks DJ	Functional imaging in relation to parkinsonian syndromes	J Neurol Sci	1993	115(1)	1-17
B22	[ICP 4]	Brooks DJ	PET studies on the early and differential diagnosis of Parkinson's disease	Neurology	1993	36(1)	27-31
B23	[ICP 5]	Brooks DJ	Isolated tremor and disruption of the nigrostriatal dopaminergic system: an 18F-dopa PET study	Neurology	1992	42(8)	1554-60
B24		Brooks DJ	Striatal D2 receptor status in patients with Parkinson's disease, striatonigral degeneration, and progressive supranuclear palsy, measured with 11C-raclopride and positron emission tomography	Ann Neurol	1992	31(2)	184-92
B25	[ICP 6]	Brooks DJ	Detection of preclinical Parkinson's disease with PET	Geriatrics	1991	46 suppl 1	25-30
B26	66	Brooks DJ	Presynaptic and postsynaptic striatal dopaminergic function in enuroacanthocytosis: a positron emission tomographic study	Ann Neurol	1991	30(2)	166-71
B27	[ICP 7]	Brooks DJ	The relationship between locomotor disability, autonomic dysfunction, and the integrity of the striatal dopaminergic system in patients with multiple system atrophy, pure autonomic failure, and Parkinson's disease,	Brain	1990	113 (pt 5)	1539-52

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			studied with PET				
B28	[ICP 8]	Brooks DJ	Differing patterns of striatal 18F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy	Ann Neurol	1990	28(4)	547-55
B29		Broussolle E	The relation of putamen and caudate nucleus 18F-Dopa uptake to motor and cognitive performances in Parkinson's disease	J Neurol Sci	1999	166(2)	141-51
B30		Broussolle E	Relief of akinesia by apomorphine and cerebral metabolic changes in Parkinson's disease	Mov Disord	1993	8(4)	459-62
B31	55	Brown WD	FluoroDOPA PET shows the nondopaminergic as well as dopaminergic destinations of levodopa	Neurology	1999	53(6)	1212-8
B32	45	Brown WD	Fluorine-18-fluoro-L-DOPA dosimetry with carbidopa treatment	J Nucl Med	1998	39(11)	1884-91
B33		Brownell AL	Combined PET/MRS brain studies show dynamic and long-term physiological changes in a primate model of Parkinson disease	Nat Med	1998	4(11)	1308-12
B34	29	Brucke T	Measurement of the dopaminergic degeneration in Parkinson's disease with [123I] beta-CIT and SPECT. Correlation with clinical findings and comparison with multiple system atrophy and progressive supranuclear palsy	J Neural Transm Suppl	1997	50	9-24
B35		Brucke T	Dopamine receptor classification, neuroanatomical distribution and in vivo imaging	Wien Klin Wochenschr	1991	103(21)	639-46
B36		Brust P	Upregulation of the aromatic amino acid	Neurobiol Dis	1999	6(2)	131-9

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			decarboxylase under neonatal asphyxia				
B37		Brust P	Simulataneous measurment of [18F]FDOPA metabolism and cerebral blood flow in newborn piglets	Int J Dev Neurosci	1998	16(5)	353-64
B38		Burn DJ	Nigral dysfunction in drug-induced parkinsonism: an 18F-dopa PET study	Neurology	1993	43 (3 Pt 1)	552-6
B39		Burn DJ	Parkinson's disease in twins studied with 18F-dopa and positron emission tomography	Neurology	1992	42(10)	1894-900
B40		Burns RS	Subclinical damage to the nigrostriatal dopamine system by MPTP as a model of preclinical Parkinson's disease: a review	Acta Neurol Scand Suppl	1991	136	29-36
C1		Calne DB	Contributions of positron emission tomography to elucidating the pathogenesis of idiopathic parkinsonism and dopa responsive dystonia	J Neural Transm Suppl	1997	50	47-52
C2		Calne DB	PET imaging in Parkinsonism	Adv Neurol	1993	60	484-7
C3		Calne DB	Dopamine agonists in Parkinson's disease	Can J Neurol Sci	1984	11 1 Suppl	221-4
C4		Caparros-Lefebvre D	PET study and neuropsychological assessment of a long-lasting post-encephalitic parkinsonism	J Neural Transm	1998	105(4-5)	489-95
C5		Caraceni TA	Problems arising during chronic treatment with L-dopa for Parkinson's disease: changes in response to treatment	J Neural Transm Suppl	1986	22	189-99
C6		Cardoso F	Peripherally induced tremor and parkinsonism	Arch Neurol (BIOA199598190778)			
C7		Carlsson A	Possible mechanisms underlying the special	Acta Neurol	1991	136	16-8

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			vulnerability of dopaminergic neurons	Scand Suppl			
C8		Carlsson A	Are "on-off" effects during chronic L-dopa treatment due to faulty feedback control of the nigrostriatal dopamine pathway?	J Neural Transm Suppl	1983	19	153-61
C9		Chan GL	Routes of administration and effect of carbidopa pretreatment on 6-[18F]fluoro-L-dopa/PET scans in non-human primates	Life Sci	1995	56(21)	1759-66
C10		Chan GL	Routine determination of [18F]-L-6-fluorodopa and its metabolites in blood plasma is essential for accurate positron emission tomography studies	Life Sci	1992	50(4)	309-18
C11	(A10)	Chan GL	Plasma L-[18F]6-fluorodopa imput function: a simplified method	J Cereb blood Flow Metab	1992	12(5)	881-4
C12		Chang MH	Resting tremor only: A variant of Parkinson's disease or of essential tremor	J Neurol Sci (BIOA1995983 63454)			
C13	65	Cherry SR	Correction and characterization of scattered events in three-dimensional PET using scanners with retractable septa	J Nucl Med	1993	34	671-8
C14	22	Cherry SR	3D PET using a conventional multislice tomograph without septa	J Comput Assist Tomogr	1991	15(4)	655-68
C15	[C15]	Cleghorn JM	Apomorphine effects on brain metabolism in enuroleptic-naïve schizophrenic patients	Pshychiatry Res	1991	40(2)	135-53
C16	61	Colosimo C	Some specific clinical features differentiate multiple system atrophy (striatonigral variety) from parkinson's disease	Arch Neurol	1995	52	294-98
C17		Cooper JM	L-dihydroxyphenylalanine and complex I deficiency in Parkinson's disease brain.	Mov Disord	1995	10(3)	295-7

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C18		Cordes M	Age-dependent decline of nigrostriatal dopaminergic function: a positron emission tomographic study of grandparents and their grandchildren	Ann Neurol	1994	3694)	667-70
C19		Cordes M	Examination of the presynaptic dopaminergic system using positron emission tomography in a family with autosomal dominant parkinsonism and dementia due to pallido-ponto-nigral degeneration	Radio Diagn	1993	34(3)	141-5
C20		Cordes M	Parametric imaging of the rate constant Ki using [18Fluoro]-L-dopa positron emission tomography in progressive supranuclear palsy	Neuroradiology	1993	3596)	404-9
C21		Cordes M	[L-18F-dopa-PET in Parkinson-plus syndromes for the detection of a disordered presynaptic dopaminergic function]	Nuklearmedizin	1992	31(2)	43-7
C22		Creveling CR	The effect of ring-fluorination on the rate of O-methylation of dihydroxyphenylalanine (DOPA) by catechol-O-methyltransferase: significance in the development of 18F-PET scanning agents	Biochem Biophys Res Commun	1985	130(3)	1123-31
C23		Cumming P	Pharmacokinetics of radiotracers in human plasma during positron emission tomography	Synapse	1999	34(2)	124-34
C24		Cumming P	Cocaine withdrawal and the cerebral influx of [18F]fluoro-L-DOPA	Neurosphychopharmacology	1999	20(4)	395-98
C25		Cumming P	Compartmental analysis of dopa decarboxylation in living brain from dynamic positron emission tomograms	Synapse	1998	29(1)	37-61
C26	44	Cumming P	Controversies arising from recent FDOPA	J Nucl Med	1997	38(8)	1267-71

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			articles				
C27		Cumming P	Metabolism and blood-brain clearance of L-3,4-dihydroxy-[3H]phenylalanine ([3H]DOPA) and 6-[18F]fluoro-L-DOPA in the rat	Biochem Pharmacol	1995	50(7)	943-6
C28		Cumming P	A kinetic analysis of 6-[18F]fluoro-L-dihydroxyphenylalanine metabolism in the rat	J Neurochem	1994	63(5)	1675-82
C29	(A13) [ICP 11]	Cumming P	Pharmacokinetics of plasma 6-[18F]fluoro-L-3,4-dihydroxyphenylalanine ([18F]Fdopa) in humans	J Cereb Blood Flow Metab	1993	13(4)	668-75
D1		Da Prada M	The pharmacology of Parkinson's disease: basic aspects and recent advances	Experientia	1984	40(11)	1165-72
D2		Danielsen EH	Cerebral 6-[(18)F]fluoro-L-DOPA (FDOPA) metabolism in pig studied by positron emission tomography	Synapse	1999	33(4)	247-58
D3		Darke AC	Critical opening pressure and ractivity of tail vessels in conscious hypertensive rats	Can J Physiol Pharmacol	1976	54(3)	314-21
D4	(A19)	Deep P	Stimulation of dopa decarboxylase activity in striatum of healthy human brain secondary to NMDA receptor antagonism with a low dose of amantadine	Synapse	1999	34(4)	313-18
D5		Deep P	On the accuracy of an [18F]FDOPA compartmental model: evidence for vesicular storage of [18F]fluorodopamine in vivo	J Neurosci Methods	1997	76(2)	157-65
D6		Defer GL	Rest tremor and extrapyramidal symptoms after midbrain haemorrhage: clinical and 18F-dopa PET evaluation	J Neurol Neurosurg Psychiatry	1994	57(8)	987-9
D7		Defer GL	Long-term outcome of unilaterally	Brain			

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			transplanted parkinsonian patients: I. Clinical approach	(BIOA199698779511)			
D8		Dejesus OT	Evaluation of fluorinated m-tyrosine analogs as PET imaging agents of dopamine nerve terminals: Comparison with 6-fluorodopa	J Nucl Med (BIOA199799523020)			
D9		Dewey RB	Long-term follow-up of levodopa responsivenss in generalized dystonia	Arch Neurol	1998	55(10)	1320-3
D10		Dewey SL	Effects of central cholinergic blockade on striatal dopamine release measured with positron emission tomography in normal human subjects	Proc Natl Acad Sci USA	1993	90(24)	11816-20
D11		Dewey SL	Striatal binding of the PET ligand 11C-raclopride is altered by drugs that modify synaptic dopamine levels	Synapse	1993	13(4)	350-6
D12		Dewey SL	Positron emission tomography (PET) studies of dopaminergic/cholinergic interactions in the baboon brain	Synapse	1990	6(4)	321-7
D13		Dhawan V	Double-blind controlled trial of human embryonic dopaminergic tissue transplants in advanced Parkinson's disease: Fluorodopa PET imaging	Neurology	1999	52 (6 Suppl 2)	A405-6
D14	(A21)	Dhawan V	Combined FDOPA and 3OMFD PET studies in Parkinson's disease	J Nucl Med	1996	37(2)	209-16
D15	(A20)	Dhawan V	Bladder wall radiation dose in humans from fluorine-18-FDOPA	J Nucl Med	1996	37(11)	1850-2
D16	9	Donnan GA	Evidence for plasticity of the dopaminergic system in parkinsonism	Mol Neurobiol	1991	5(2-4)	421-33
D17		Doudet DJ	6-[18F]Fluoro-L-DOPA PET studies of the	Synapse	1998	29(3)	225-32

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			turnover of dopamine in MPTP-induced parkinsonism in monkeys				
D18		Doudet DJ	Effects of catechol-O-methyltransferase inhibition on the rates of uptake and reversibility of 6-fluoro-L-Dopa trapping in MPTP-induced parkinsonism in monkeys	Neuropharmacology	1997	36(3)	363-71
D19		Doudet DJ	6-18F-L-DOPA imaging of the dopamine neostriatal system in normal and clinically normal MPTP-treated rhesus monkeys	Exp Brain Res	1989	78	69-80
D20		Dunn BB	A single column, rapid quality control procedure for 6-[18F]fluoro-L-dopa and 6-[18F]fluorodopamine PET imaging agents	Int J Rad Appl Instrum	1991	18(2)	209-13
E1		Edling C	Do organic solvents induce changes in the dopamineric system? Positron emission tomography studies of occupationally exposed subjects.	Int Arch Occup Environ Health	1997	70(3)	180-6
E2		Edling C	Positron emission tomography studies of healthy volunteers—no effects on the dopamine terminals an synthesis after short-term exposure to toluene	Hum Exp Toxicol	1997	1693)	171-6
E3	(A26)	Eidelberg D	Early differential diagnosis of Parkinson's disease with 18F-fluorodeoxyglucose and positron emission tomography	Neurology	1995	45(11)	1995-2004
E4	(A25) [ICP 14]	Eidelberg D	Striatal 18f-dopa uptake: absence of an aging effect	J Cereb Blood Flow Metab	1993	13(5)	881-8
E5		Eidelberg D	Positron emission tomographic findings in Filipino X-linked dystonia-parkinsonism	Ann Neurol	1993	3492)	185-91

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E6	12	Eidelberg D	Positron emission tomography studies in parkinsonism	Neurol Clin	1992	10(2)	421-33
E7	(A24)	Eidelberg D	The metabolic anatomy of Parkinson's disease: complementary [18F]fluorodeoxyglucose and [18F] fluorodopa positron emission tomographic studies	Mov Disord	1990	5(3)	203-13
E8		Ekesbo A	Dopamine autoreceptor function is lost in advanced Parkinson's disease	Neurology	1999	52(1)	120-5
E9		Ernst M	High midbrain [18F]DOPA accumulation in children with attention deficit hyperactivity disorder	Am J Psychiatry	1999	156(8)	1209-15
E10		Ernst M	High presynaptic dopaminergic activity in children with Tourette's disorder	J Am Acad Child Adolesc Psychatry	1999	38(1)	86-94
E11		Ernst M	DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [F-18}fluorodopa positron emission tomographic study	J Neurosci	1998	18(15)	5901-7
E12		Ernst M	Presynaptic dopaminergic deficits in Lesch-Nyhan disease	N Eng J Med	1996	334(24)	1568-72
F1		Fahn S	Controversies in the therapy of Parkinson's disease	Adv Neurol	1996	69	477-86
F2		Fallen EL	Recovery rates of regional sympathetic reinnervation and myocardial blood flow after acute myocardial infarction	Am Heart J	1999	137(5)	863-9
F3		Farde L	Brain imaging of schizophrenia – The dopamine hypothesis	Psiquiatr Biol	1998	6(2)	87-91

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F4		Farde L	The advantage of using positron emission tomography in drug research	Trends Neurosci	1996	19(6)	211-14
F5	37	Fernley JM	Ageing and Parkinson's disease: substantia nigra regional selectivity	Brain	1991	114	2283-301
F6		Firnau G	New 18F tracers for the investigation of brain functions	Acta Radiol Suppl	1990	374	37-41
F7		Fischman AJ	Rapid detection of Parkinson's disease by SPECT with altropane: a selective ligand for dopamine transporters	Synapse	1998	29(2)	128-41
F8		Fowler JS	Monoamine oxidase B (MAO B) inhibitor therapy in Parkinson's disease: the degree and reversibility of human brain MAO B inhibition by Ro 19 6327	Neurology	1993	43(10)	1984-92
F9		Freed CR	Survival of implanted fetal dopamine cells and neurologic improvement 12 to 46 months after transplantation for Parkinson's disease	N Engl J Med	1992	327(22)	1549-55
F10		Freed CR	Transplantation of human fetal dopamine cells for Parkinson's disease. Results at 1 year	Arch Neurol	1990	47(5)	505-12
F11		Freeman TB	Bilateral fetal nigral transplantation into the postcommisural putamen Parkinson's disease	Ann Neurol	1995	38(3)	379-88
F12		Frey KA	Presynaptic monoaminergic vesicles in Parkinson's disease and normal aging	Ann Neurol	1996	40(6)	873-84
F13		Friedman J	Recent research advances in Parkinson's disease: Part I	R I Med J	1986	69(7)	319-22
F14	23	Friston KJ	Comparing functional (PET) images: the assessment of significant change	J Cereb Blood Flow Metab	1991	11	690-9
F15		Frost JJ	Positron emission tomographic imaging of	Ann Neurol	1993	34(3)	423-31

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			the dopamine transporter with 11C-WIN 35,428 reveals marked declines in mild Parkinson's disease				
F16		Fujii R	[Fluorine-18 labeled 6-fluoro-L-dopa: systematization and evaluation of its usefulness.]	Kaku Igaku	1997	34(11)	1055-61
G1	[G1]	Garnett ES	Central dopaminergic pathways in hemiparkinsonism examined by positron emission tomography	Can J Neurol Sci	1984	11 (1 Suppl)	174-9
G2	3	Gelb DJ	Diagnostic criteria for parkinson disease	Arch Neurol	1999	56	33-9
G3		Gerfen CR	Molecular neuroanatomic mechanisms of Parkinson's diasease: a proposed therapeuti approach	Neurol Clin	1992	10(2)	435-49
G4	1	Gibb WRG	Accuracy in the clinical diagnosis of parkinsonian syndromes	Postgrad Med J	1988	64	345-51
G5	[G5]	Gjedde A	Striatal L-dopa decarboxylase activity in Parkinson's disease in vivo: implications for the regulation of dopamine synthesis	J Neurochem	1993	61(4)	1538-41
G6	55	Gjedde A	Dopa decarboxylase activity of the living human brain	Proc Natl Adad Sci USA	1991	88(7)	2721-5
G7		Goldman S	[Positron emission tomography in akinetic rigidity syndrome]	Rev Med Brux	1995	16(6)	399-403
G8		Goldstein DS	Sympathetic cardioneuropathy in dysautomias	New Engl J Med	1997	336(10)	696-702
G9		Goldstein DS	Metabolic fate of the sympathoneural imaging agent 6-[18f]fluorodopamine in humans	Clin Exp Hypertens	1997	19(1-2)	155-51
G10		Goldstein DS	6-(F-18)fluorodopamine pharmacokinetics	J Nucl Med	1994	35(6)	964-73

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			and dosimetry in humans				
G11		Goldstein DS	Chemical mediators of autonomic nervous system activity	Curr Opin Neurol Neurosurg	1993	6(4)	524-6
G12		Gunther I	Positron emission tomography in drug evaluation: influence of three different catechol-O-methyltranseferase inhibitors on metabolism of [NCA] 6-18F]flouro-L-dopa in rhesus monkey	Nucl Med Biol	1995	22(7)	921-7
G13		Guttman M	Administration of the new COMT inhibitor OR-611 increases striatal uptake of fluorodopa	Mov Disord	1993	8(3)	298-304
G14	[G14]	Guttman M	Dopamine receptors in Parkinson's disease	Neurol Clin	1992	10(2)	377-86
G15		Guttman M	Asymptomatic striatal dopamine depletion: PET scans in unilateral MPTP monkeys	Synapse	1988	2(5)	469-73
G16		Guttman M	L-dopa reverses the elevated density of D2 dopamine receptors in Parkinson's diseased striatum	J Neural Transm	1985	64(2)	93-103
H1	70	Hachinski V	Levodopa Toxicity	Arch Neurol	2000	57	410
H2		Hagell P	Sequential bilateral transplantation in Parkinson's disease: Effects of the second graft	Brain	1999	122(6)	1121-32
H3		Hagglund J	Dopamine receptor properties in Parkinson's disease and Huntington's chorea evaluated by positron emission tomography using 11C-N-methyl-spiperone	Acta Neurol Scand	1987	75(2)	87-94
H4		Hagglund J	Regional kinetics of [11C]methylspiperone in the brain studied by positron emission	Adv Neurol	1987	45	99-101

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			tomography in patients with Parkinson's disease				
H5		Harder S	Levodopa PK-PD-analysis in relation to (18F)F-Dopa-PET in patients with Parkinsons disease	Clin Pharmacol Ther	1999	65(2)	169
H6	63	Hardie RJ	Measuring the rate of progression and estimating the preclinical period Parkinson's disease with [18F] dopa PET	J Neurol Neurosurg Psychiatry	1999	66(2)	256
H7		Hartvig P	Amphetamine effects on dopamine release and synthesis rate studied in the Rhesus monkey brain by positron emission tomography	J Neural Tansm	1997	104(4-5)	329-39
H8		Hartvig P	Brain Kinetics of L-beta-carbon-11 dopa in humans studied by positron emission tomography	J Neural Transm	1991	86(1)	25-42
H9		Hassan MN	Dopamine receptors in Parkinson's disease	Prog Neuropsychopharmacol Biol Psychiatry	1988	12(2-3)	173-82
H10		Hauser RA	Long-term evaluation of bilateral fetal nigral transplantation in Parkinson disease	Arch Neurol	1999	56(2)	179-87
H11		Heiss WD	F-Dopa as an amino acid tracer to detect brain tumors	J Nucl Med	1996	37(7)	1180-2
H12		Hietala J	Depressive symptoms and presynaptic dopamine function in neuroleptinaive schizophrenia	Schizophr Res	1999	35(1)	41-50
H13		Hietala J	Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients	Lancet	1995	346 (8983)	1130-1

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H14		Hoegerle S	Imaing of a metastatic gastrointestinal carcinoid by F-18-DOPA positron emission tomography	Nuklearmedizin	1999	38(4)	127-30
H15	54	Hoehn MM	Parkinsonism: onset, progression, and mortality	Neurology	1967	17	427-42
H16		Hoffer BJ	Eighteen-month course to two patients with grafts of fetal dopamine neurons for severe Parkinson's disease	Exp Neurol	1992	118(3)	243-52
H17	(A30)	Hoffman JM	The effects of carbidopa administration on 6-[18F]fluoro-L-dopa kinetics in positron emission tomography	J Nucl Med	1992	3398)	1472-7
H18		Holthoff VA	Discordnat twins with Parkinson's disease: positron emission tomography and early signs of impaired cognitive circuits	Ann Neurol	1994	3692)	176-82
H19		Holthoff VA	Functional effects of striatal dysfunction in Parkinson disease	Arch Neurol (BIOA1997994 59959)			
H20		Hornykiewicz O	Brain monoamines and parkinsonism	Natl Inst Drug Abuse Res Monogr Ser	1975	3	13-21
H21		Horstink MW	L-dopa in Parkinson's disease	Neurology	1991	41(10)	1709
H22	(A31)	Hoshi H	6-[18F]fluoro-L-dopa metabolism in living human brain: a comparison of six analytical methods	J Cereb Blood Flow Metab	1993	13(1)	57-69
H23		Huang SC	Modelling approach for separating blood time-activity curves in positron emission tomographic studies	Phys Med Biol	1991	36(6)	749-61
H24	(B1)	Huang SC	Kinetics and modeling of L-6-[18f]fluoro-	J Cereb Blood	1991	11(6)	898-913

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	[ICP 15]		dopa in human positron emission tomographic studies	Flow Metab			
H25	16	Hughes AJ	The clinical features of Parkinson's disease in 100 histologically proven cases	Adv Neurol	1993	60	595-9
H26	35/62	Hughes AJ	Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases	J Neurol Neurosurg Psychology	1992	55	181-4
H27	34	Hughes AJ	What features improve the accuracy of clinical diagnosis in Parkinson's disease: A clinicopathologic study	Neurology	1992	42	1142-6
I1	[I1]	Iacoboni M	Emission tomography contribution to clinical neurology	Clin Neurophysiol	1999	110(1)	2-23
I2		Ichise M	Physiologic modeling of PET data: quantitative conflict and challenge	J Nucl Med	1997	38(8)	1266-7
I3		Ilgin N	Functional imaging of neurotransmitter systems in movement disorders	Q J Nucl med	1998	42(3)	179-92
I4		Indo T	[Striatal dopamine availability in Parkinson's disease—with reference to the wearing-off phenomenon]	Rinsho shinkeigaku	1984	24(10)	1008-16
I5		Inoue Y	Atlas of dopamine receptor images (PET) of the human brain	J Comput Assist Tomogr	1985	9(1)	129-40
I6	(B4) [ICP 16]	Ishikawa T	Clinical significance of striatal DOPA decarboxylase activity in Parkinson's disease	J Nucl Med	1996	37(2)	216-22
I7	(B3)	Ishikawa T	Comparative nigrostriatal dopaminergic imaging with iodine-123-beta CIT-FP/SPECT and fluorine-18-FDOPA/PET	J Nucl med	1996	37(11)	1760-5
I8	(B2)	Ishikawa T	Fluorodopa positron emission tompgraphy	J Cereb Blood	1996	1695)	854-63

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			with an inhibitor of catechol-O-methyltransferase: effect of the plasma 3-O-methyldopa fraction on data analysis	Flow Metab			
I9		Ishiwata K	Synthesis and evaluation of an 18F-labeled dopa prodrug as a PET tracer for studying brain dopamine metabolism	Nucl Med Biol	1996	2393)	295-301
I10		Ishiwata K	Selective 2-[18F]fluorodopa uptake for melanogenesis in murine metastatic melanomas	J Nucl Med	1991	32(1)	95-101
I11	58	Ito K	Statistical parametric mapping with 18F-dopa PET show bilaterally reduced striatal and nigral dopaminergic function in early Parkinson's disease	J Neurol Neurosurg Psychiatry	1999	66(6)	754-8
I12		Itoh M	[In vivo visulaization of neurotransmitter function in the human brain by PET]	No To hattatsu	1995	27(2)	146-52
I13	(B7)	Itoh M	Assessment of dopamine metabolism in brain of patients with dementia by means of 18F-fluorodopa and PET	Ann Nucl Med	1994	8(4)	245-51
J1	71	Jankovic J	The evolution of diagnosis in early Parkinson disease	Arch Neurol	2000	57	369-72
K1	2	Kaakkola S	General properties and clinical possibilities of new selectvie inhibitor of catechol O-methyltranseferase	Gen Pharmacol	1994	2595)	813-24
K2		Kaneko S	Enzymatic synthesis of no-carrier-added 6-[18F]fluoro-L-dopa with beta-tyrosinase	Appl Radiat Isot	1999	50(6)	1025-32
K3		Kapfhammer HP	[Dopamine agonists in the therapy of parkinson syndrome]	Nervenarzt	1985	56(2)	69-81
K4		Kapur S	Role of the dopaminergic system in	Biol Psychiatry	1992	32(1)	1-17

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			depression				
K5	30	Karbe H	Positron emission tomography in degenerative disorders of the dopaminergic system	J Neural Transm Park dis Dement Sect	1992	4(2)	121-30
K6		Kempster PA	Dietary factors in the management of Parkinson's disease	Nutr Rev	1994	52 (2 Pt 1)	51-8
K7		Kilbourn MR	In vivo radiotracers for vesicular neurotransmitter transporters	Nucl Med Biol	1997	24(7)	615-9
K8		Kim JW	Manganese induced parkinsonism: a case report	J Korean Med Sci	1998	13(4)	437-9
K9		Kim Y	Positron emission tomography (PET) in differentiating manganism from idiopathic parkinsonism	J Occupational Health	1999	41(2)	91-4
K10		Kim Y	Idiopathic parkinsonism with superimposed manganese exposure: utility of positron emission tomography	Neurotoxicology	1999	20(2-3)	249-52
K11	7	Kish SJ	Striatal 3,4-dihydroxyphenylalanine decarboxylase in aging: disparity between postmortem and positron emission tomography studies?	Ann Neurol	1995	38(2)	260-4
K12	33	Kish SJ	Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease	N Engl J Med	1988	318	876-80
K13		Kishore A	Presynaptic nigrostriatal function in genetically tested asymptomatic relatives from the pallido-ponto-nigral degeneration family	Neurology	1996	47(6)	1588-90
K14		Koide T	Three Cases of clinically diagnosed	Rinsho	1995	35(11)	1184-90

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			corticobasal degeneration –neuroimaging studies with MRI, SPECT, and PET	Shinkeigaku			
K15	11	Koller WC	When does Parkinson's disease begin?	Neurology	1992	42 (4sup4)	27-31
K16		Kopin IJ	In-vivo quantitative imaging of catecholaminergic nerve terminals in brain and peripheral organs using positron emission tomography (PET)	J Neural Transm Suppl	1990	32	19-27
K17		Kordower JH	Fetal nigral grafts survive and mediate clinical benefit in a patient with Parkinson's disease	Mov Disord	1998	13(3)	383-93
K18		Kordower JH	Neuropathological evidence of graft survival and striatal reinnervation after the transplantation of fetal mesencephalic tissue in a patient with parkinson's disease	N Engl J Med	1995	332(17)	1118-24
K19		Kubota R	Active melanogenesis in non-S phase melanocytes in B16 melanomas in vivo investigated by double-tracer microautoradiography with 18F-fluorodopa and 3H-thymidine	Br J Cancer	1992	66(4)	614-8
K20		Kung HF	Overview of radiopharmaceuticals for diagnosis of central nervous disorders	Crit Rev Clin Lab Sci	1991	28(4)	269-86
K21		Kuno S	Dilemma in the treatment of Parkinson's disease with L-dopa	Eur Neurol	1994	34 Suppl 3	17-9
K22		Kuwabara H	Blood-to-brain transport of large neutral amino acids studied with (18F)fluoro-DOPA ((18F)FDOPA and PET	J Nucl	1998	39 (5 Suppl)	43P
K23	(B11)	Kuwabara H	Regional striatal DOPA transport and	J Nucl Med	1995	36(7)	1226-31

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			decarboxylase activity in Parkinson's disease				
K24	(B10) [ICP 17]	Kuwabara H	Human striatal L-dopa decarboxylase activity estimated in vivo using 6-[18F]fluoro-dopa and positron emission tomography: error analysis and application to normal subjects	J Cereb Blood Flow Metab	1993	13(1)	43-56
K25		Kuzuhara S	[Recent therapeutic advances in geriatric neurology]	Nippon Ronen Igakkai Zasshi	1992	29(7-8)	531-9
L1	[ICP 18]	Laihinen A	[18F]-6-fluorodopa PET scanning in Parkinson's disease after selective COMT inhibition with nitecapone (OR-462)	Neurology	1992	42(1)	199-203
L2		Laihinen AO	PET studies on brain monoamine transporters with carbon-11-beta-CIT in Parkinson;s disease	J Nucl Med	1995	36(7)	1263-7
L3		Laihinen AO	PET studies on dopamine D1 receptors in the human brain with carbon-11-SCH 39166 and carbon-11-NNC 756	J Nucl Med	1994	35(12)	1916-20
L4	39	Lang AE	Parkinson's disease (First of Two Parts)	N Engl J Med	1998	339(15)	1044-53
L5	40	Lang AE	Parkinson's disease (Second of Two Parts)	N Engl J Med	1998	339(16)	1130-43
L6		Lang AE	Hemiatrophy, juvenile-ondet exertional alternating leg paraesis, hypotonic and hemidystonia and adult-onset hemiparkinsonism: the spectrum of hemiparkinsonism-hemiatrophy syndrome	Mov Disord	1995	1994)	489-95
L7	53	Lang AE	Dopa-responsive parkinsonism with normal 6[18F]-fluorodopa positron emission tomography scans	Ann Neurol	1990	28(4)	592-3
L8		Lee CS	Heterogeneous severity of lesions in the striatum of patients with Parkinson's disease:	Neurology	1998	50 (4 suppl	A391-2

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			In vivo PET studies using dihydrotetrabenazine, methyphenidate and F-DOPA			4)	
L9	[ICP 21]	Leender KL	Pathophysiology of movement disorders studied using PET	J Neural Transm Suppl	1997	50	39-46
L10		Leenders KL	The nigrostriatal dopaminergic system assessed in vivo by positron emission tomography in healthy volunteer subjects and patients with Parkinson's disease	Arch Neurol	1990	47(12)	1290-8
L11		Leenders KL	Parkinson's disease and PET tracer studies	J Neural Transm Suppl	1988	27	219-25
L12	[ICP 20]	Leenders KL	Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography	J Neurol Neurosurg Psuchiatry	1986	49(8)	853-60
L13	(B12)	Leger G	Effect of catechol-O-methyltranseferase inhibition on brain uptake of [18F]fluorodopa: implications for compartmental modelling and clinical usefulness	Synapse	1998	30(4)	351-64
L14	[L14]	Lenzi GL	PET studies of the dopaminergic system	J Nucl Med Allied Sci	1990	34(1)	1-9
L15		Levivier M	Intracerebral transplantation of fetal ventral mesencephalon for patient with advanced Parkinson's disease. Methodology and 6-month to 1-year follow-up in 3 patients	Stereoract Funct Neursurg	1997	69(1-4 Pt 2)	99-111
L16	(B13)	Lin KP	Automated image registration for FDOPA PET studies	Phys Med Biol	1996	41912)	2775-88
L17		Lindvall O	Grafts of fetal dopamine neurons survive and	Science	1990	247	574-7

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			improve motor function in Parkinson's disease			(4942)	
L18		Lindvall O	Evidence for long-term survival and function of dopaminergic grafts in progressive Parkinson's disease	Ann Neurol (BIOA199497176797)			
L19	42	Louis ED	Comparison of extrapyramidal features in 31 pathologically confirmed cases of diffuse Lewy body disease and 34 pathologically confirmed cases of Parkinson's disease	Neurology	1997	48	376-80
L20	(B14)	Luxen A	Production of 6-[18F]fluoro-L-dopa and its metabolism in vivo—a critical review	Int J Rad Appl Instrum B	1992	19(2)	149-58
L21		Luxen A	Remote, semiautomated production of 6-[18F]fluoro-L-dopa for human studies with PET	Int J Rad Appl Instrum	1990	41(3)	275-81
M1		Marie RM	Quantification of dopamine transporter density in monkeys by dynamic PET imaging of multiple injections of 11C-CFT	Synapse	1996	24(3)	262-72
M2		Marie RM	PET imging of neocortical monoaminergic terminals in Parkinson's disease	J Neural Transm Park Dis Dement Sect	1995	9(1)	55-71
M3	41	Mark MH	Levodopa-nonresponsive Lewy body parkinsonism: Calinicopathologic study of two cases	Neurology	1992	42	1323-7
M4		Martin WR	Assessment of fetal tissue transplantation in Parkinson's disease: does PET play a role?	Neurology	1994	44(10)	1777-80
M5	[ICP 22]	Martin WR	Nigrostriatal function in humans studied with positron emission tomography	Ann Neurol	1989	26	535-42

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M6		Martin WR	Parkinson's disease: positron emission tomographic studies	Semin Neurol	1989	9(4)	345-50
M7		Maziere B	PET radioligands for dopamine receptors and re-uptake sites: chemistry and biochemistry	Int J Rad Appl Insturm	1992	19(4)	497-512
M8	(B15)	Meguro K	Striatal dopamine metabolism correlated with frontotemporal glucose utilization in Alzheimer's disease: a double-tracer PET study	Neurology	1997	55(8)	2148-55
M9	(B16)	Mejia AA	Absorbed dose estimates in positron emission tomography studies based on the administration of 18f-labeled radiopharmaceuticals	J Radiat Res	1991	32(3)	243-61
M10		Melamed E	Interactions of exogenous L-dopa with nigrostriatal dopaminergic neurons in Parkinson's disease	Adv Neurol	1990	53	61-6
M11		Melamed E	Role of the nigrostriatal dopaminergic neurons in meidating the effect of exogenous L-dopa in Parkinson's disease	Mt Sinai j Med	1988	55(1)	35-42
M12		Melega WP	Ethological and 6-[18F]fluoro-L-DOPA-PET profiles of long-term vulnerability to chronic emphetamine	Behav Brain Res	1997	84(1-2)	259-68
M13		Melega WP	Recovery of striatal dopamine function after acute amphetamine- and methamphetamine-induced neurotoxicity in the vervet monkey	Brain Res	1997	766(1-2)	113-20
M14		Melega WP	Longitudinal behavioral and 6-[18F]fluoro-L-DOPA-PET assessment in MPTP-hemiparkinsonian monkeys	Exp Neurol	1996	141(2)	318-29
M15		Melega WP	6-[18F]fluoro-L-DOPA-PET Studies show	Synapse	1996	22(1)	63-9

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			partial reversibility of long-term effects of chronic amphetamine in monkeys				
M16	(B19)	Melega WP	L-6-[18F]fluoro-dopa metabolism in monkeys and humans: biochemical parameters for the formulation of tracer kinetic models with positron emission tomography	J Cereb Blood Flow Metab	1991	11(6)	890-7
M17		Melega WP	6-[18F]fluoro-L-DOPA metabolism in MPTP-treated monkeys: assessment of tracer methodologies for positron emission tomography	Brain Res	1990	543	271-6
M18	(B18) [ICP 23]	Melega WP	The effects of carbidopa on the metabolism of 6-[18F]fluoro-L-dopa in rats, monkeys and humans	Life Sci	1990	47(2)	149-57
M19		Melega WP	Comparative in vivo metabolism of 6-[18F]fluoro-L-dopa an d[3H]L-dopa in rats	Biochem Pharmacol	1990	39(12)	1843-60
M20		Menza MA	Personality correlates of [18f]dopa striatal uptake: results of positron emission tomography in Parkinson's disease	J Neuropsychiatry Clin Neurosci	1995	7(2)	176-9
M21		Mercuri NB	Physiology and pharmacology of dopamine D2-receptors: their implications in dopamine-substitute therapy for Parkinsons's disease	Neurology	1989	39(8)	1106-8
M22		Miller GW	Immunochemical analysis of dopamine transporter protein in Parkinson's disease	Ann Neurol	1997	41(4)	530-9
M23		Minami T	Different patterns of [18F]dopa uptake in siblings with hereditary dentato-rubro-pallido-luysian atrophy	Brain Dev	1994	16(4)	335-8
M24		Momose T	[Striatal dopamine D2 receptor in Parkinson	Nippon Rinsho	1997	55(1)	227-32

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			disease and its related disorders assessed by C-11 NMSP and PET]				
M25		Morris ED	Quantification of dopamine transporter density in monkeys by dynamic PET imaging of multiple injections of 11C-CFT	Synapse	1996	24(3)	262-72
M26	60	Morrish PK	Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET	J Neurol Neurosurg Psychiatry	1998	64(3)	314-9
M27		Morrish PK	Parkinson's disease is not a long-latency illness	Mov Disord	1997	12(6)	849-54
M28	51 [ICP 26]	Morrish PK	An [18F]dopa PET and clinical study of the rate of pregression in Parkinson's disease	Brain	1996	119	585-91
M29	52	Morrish PK	Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease	Brain	1996	119	2097-2103
M30	15	Morrish PK	The rate of progression of Parkinson's disease. A longitudinal [18F]DOPA PET study	Adv Neurol	1996	69	427-31
M31	[ICP 27]	Morrish PK	Clinical and [18F] dopa PET findings in early Parkinson's disease	J Neurol Neurosurg Psychiatry	1995	59(6)	597-600
M32	27	Muenter MD	Hereditary form of parkinsonism—dementia	Ann Neurol	1998	43(6)	768-81
M33		Muller T	2-[123I]-iodolisuride SPET visualizes dopaminergic loss in de-novo parkinsonian patients: is it a marker of striatal pre-synaptic degeneration?	Nucl Med Commun	1997	18(12)	1115-21
M34		Murali D	[18F]fluoro-beta-fluromethylene-m-tyrosine analogs, potential PET agents for presynptic	Int J Rad Appl Instrum	1992	43(8)	969-77

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			dopamine terminals: synthesis and spectroscopic characterization				
N1		Nagasawa H	[PET study using 6-[18F]fluorodopa metabolism in early and late onset of Parkinson's disease studied by positron emission tomography]	Nippon Rinsho	1997	55(1)	213-7
N2		Nagasawa H	PET study of cerebral glucose metabolism and fluorodopa uptake in patients with corticobasal degeneration	J Neurol Sci	1996	139(2)	210-7
N3	18	Nagasawa H	Brain 6-[18F]fluorodopa metabolism in early and late onset of Parkinson's disease studied by positron emission tomography	J Neurol Sci	1996	144(1-2)	70-6
N4	20	Nagasawa H	6-[18F]fluorodopa metabolism in patients with hemiparkinsonism studied by positron emission tomography	J Neurol Sci	1993	115(2)	136-43
N5	[ICP 28]	Nahmias C	Striatal dopamine distribution in parkinsonian patients during life	J Neurol Sci	1985	69	223-30
N6		Naumann M	[123I]beta-CIT single-photon emission tomography in DOPA-responsive dystonia	Mov Diord	1997	12(3)	448-51
N7		Nygaard TG	Long-term treatment response and fluorodopa positron emission tomographic scanning of parkinsonism in a family with dopa-responsive dystonia	Ann Neurol	1992	32(5)	603-8
O1		Okada A	PET scan study on the dopaminergic system in a Japanese patient with hereditary progressive dystonia (Segawa's disease). Case report	Adv Neurol	1993	60	591-4
O2		Opacka-Juffry	L-dihydroxyphenylalanine and its	Mov Disord	1995	10(3)	241-9

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		J	decarboxylase: new ideas on their neuroregulatory roles				
O3		Oreland L	Monoamine oxidase, dopamine and Parkinson's disease	Acta Neurol Scand Suppl	1991	136	60-5
O4		Orihara H	Three-Dimensional positron emission tomography imaging system and its application for medical use	Nippon Rinsho	1997	55(8)	2148-55
O5		Osman L	The effect of peripheral catechol-O-methyl transferase inhibitor OR-611 (entacapone) on the metabolism of 6-(18F)fluoro-L-dopa	J Label Compd Radiopharm	1994	35	543-45
O6	25	Otsuka M	Differentiating between multiple system atrophy and Parkinson's disease positron emission tomography with 18F-dopa and 18F-FDG	Ann Nucl Med	1997	11(3)	251-7
O7	19	Otsuka M	Differences in the reduced 18F-Dopa uptakes of the caudate and the putamen in Parkinson's disease: correlations with the three main symptoms	J Neurol Sci	1996	136(1-2)	169-73
O8		Otsuka M	Nigrofrontal dopaminergic function as assessed by 18F-dopa PET	Nucl Med Commun	1995	16(12)	1021-5
O9		Otsuka M	Cerebral glucose metabolism and striatal 18F-dopa uptake by PET in cases of chorea with or without dementia	J Neurol Sci	1993	115(2)	153-7
O10		Otsuka M	Increased striatal 18F-dopa uptake and normal glucose metabolism in idiopathic dystonia syndrome	J Neurol Sci	1992	111(2)	195-9
O11		Otsuka M	Striatal blood flow, glucose metabolism and 18f-dopa uptake: difference in Parkinson's	J Neurol Neurosurg	1991	54(10)	898-904

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			disease and atypical Parkinsonism	Psychiatry			
O12		Otsuka M	Striatal 18F-Dopa uptake and brain glucose metabolism by PET in patients with syndrome of progressive ataxia	J Neurol Sci (BIOA199497407531)			
P1		Pascual J	Neurochemistry of Parkinson's disease and parkinsonism plus	Rev Neurol	1997	25 Suppl 2	S141-6
P2	[ICP 29]	Pate BD	The reproducibility of striatal uptake data obtained with positron emission tomography and fluorine-18-L-6-fluorodopa tracer in non-human primates	J Nucl Med	1991	32(6)	1246-51
P3		Pearce RK	Dopamine uptake sites and dopamine receptors in Parkinson's disease and schizophrenia	Eur Neurol	1990	30 Suppl 1	9-14
P4		Peppard RF	Parkinsonism with neuroacanthocytosis	Can J Neurol Sci	1990	17(3)	298-301
P5		Peschanski M	Bilateral motor improvement and alteration of L-dopa effect in two patients with Parkinson's disease following intrastriatal transplantation of foetal ventral mesencephalon	Brain	1994	117 (Pt 3)	487-99
P6		Petruk KC	Treatment of refractory Parkinson's disease with adrenal medullary autografts utilizing two-stage surgery	Prog Brain Res	1990	82	671-6
P7	17	Piccini P	Etiology of Parkinson's disease: contributions from 18F-DOPA positron emission tomography	Adv Neurol	1999	80	227-31
P8		Piccini P	Dopaminergic function in familial Parkinson's disease: a clinical and 18F-dopa	Ann Neurol	1997	41(2)	222-9

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			positron emission tomography study				
P9		Piccini P	Alterations in opioid receptor binding in Parkinson's disease patients with levodopa-indued dyskinesias	Ann Neurol	1997	42(5)	720-6
P10	28	Piccini P	PET studies of the striatal dopaminergic system in Parkinson's disease (PD)	J Neural Transm Suppl	1995	45	123-31
P11		Pietrzyk U	An interactive technique for three-dimensional image registration: validation for PET, SPECT, MRI and CT brain studies	J Nucl Med	1994	35(12)	2011-8
P12		Price JC	Measurement of benzodiazepine receptor number and affinity in humans using tracer kinetic modeling, positron emission tomography, and carbon-11 flumazenil	J Cereb Blood Flow Metab (BIOA199396068320)			
P13		Przeborski S	Brain glucose metabolism and dopamine D2 receptor analysis in a patient with hemiparkinsonism-hemiatrophy syndrome	Mov Disord	1993	8(3)	391-5
P14	(B25)	Przedborski S	Nigrostriatal dopaminergic function in familiar amyotrophic lateral sclerosis patients with and without copper/zinc superoxide dismutase mutations	Neurology	1996	47(6)	1546-51
P15	(B24)	Przedborski S	Metabolic topography of the hemiparkinsonism-hemiatrophy syndrome	Neurology	1994	44(9)	1622-8
P16		Psylla M	Cerebral 6-{18F]fluoro-L-FDOPA uptake in rhesus monkey: pharmacological influence of aromatic amino acid decarboxylase (AAAD) and catechol-O-methyltransferase (COMT) inhibition	Brain Res	1997	767(1)	45-54
P17		Pycock CJ	Central dopaminergic receptor	J Neurol Sci	1977	31(1)	113-21

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			supersensitivity and its relevance to Parkinson's disease				
R1	59	Rajput AH	Is levodopa toxic to human substantia nigra?	Mov Disord	1997	12(5)	634-8
R2	43	Rajput AH	Accuracy of clinical diagnosis in Parkinsonism – A prospective study	Can J Neurol Sci	1991	18	275-8
R3	38	Rajput AH	Levodopa efficacy and pathological basis of parkinson syndrome	Clin Neuropharm	1990	13(6)	553-8
R4	18	Rakshi JS	Frontal, midbrain and striatal dopaminergic function in early and advanced Parkinson's disease A 3D [(18)F]doap-PET study	Brain	1999	122(pt9)	1637-50
R5		Rakshi JS	Statistical parametric mapping of three dimensional 18F-dopa PET in early and advanced Parkinson's disease	Mov Disord	1996	11 (Sup 1)	147
R6		Reddy GN	Quality assurance and quality control methods for animal and human applications of no-arrier-added 6-[18F]fluorodopa for PET investigations of dopaminergic systems	Appl Radiat Isot	1993	44(7)	993-8
R7		Reith J	Blood-brain transfer and metabolism of 6-[18F]fluoro-L-dopa in rat	J Cereb Blood Flow Metab	1990	10(5)	707-19
R8		Remy P	Relationships between (18F)-fluorodopa uptake in the caudate nucleus and cognitive function in advanced Parkinson's disease	Soc Neurosci Abs	1998	24(1-2)	1221
R9		Remy P	Peduncular 'rubral' tremor and dopaminergic denervation: a PET study	Neurology	1995	45 (3 Pt 1)	472-7
R10		Remy P	Clinical correlates of [18F]fluorodopa uptake in five grafted parkinsonian patients	Ann Neurol	1995	38(4)	580-8
R11		Remy P	Striatal dopaminergic denervation in pallidopyramidal disease demonstrated by	Ann Neurol	1995	38(6)	954-6

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			positron emission tomography				
R12		Rinne JO	Positron emission tomography studies on the dopamineric system and striatal opioid binding in the olivepontocerebellar atrophy variant of multiple system atrophy	Ann Neurol	1995	37(5)	568-73
R13		Rinne JO	PET examination of the monoamine transporter with [11C]beta-CIT and [11C]beta-CFT in early Parkinson's disease	Synapse	1995	21(2)	97-103
R14		Rinne JO	Decrease in human striatal dopamine D2 receptor density with age: a PET study with [11C]raclopride	J Cereb Blood Flow Metab	1993	13(2)	310-4
R15		Rinne JO	PET study on striatal dopamine D2 receptor changes during the progression of early Parkinson's disease	Mov Disord	1993	8(2)	134-8
R16		Rinne JO	Nigral degenration in Parkinson's disease in relation to clinical features	Acta Neurol Scand Suppl	1991	136	87-90
R17		Rinne JO	PET demonstrates different behavior of striatal dopamine D-1 and D-2 receptors in early Parkinson's disease	J Neurosci Res	1990	27(4)	494-99
R18		Rinne UK	Positron emission tomography demonstrated dopamine D2 receptor supersensitivity in the striatum of patients with early Parkinson's disease	Mov Disord	1990	5(1)	55-9
R19		Rose S	Fluctuations in response to L-dopa in Parkinson's disease may be explained by changes in striatal dopamine turnover	Br J Pharmacol	1989	98 Suppl	816P
R20		Rosenow F	Neurological sequelae of cyanide intoxication: The patterns of clinical,	Ann Neurol (BIOA1996986			

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			magnetic resonance imaging, and positron emission tomography findings	02114)			
R21		Rossor MN	Progressive frontal gait disturbance with atypical Alzheimer's disease and corticobasal degeneration	J Neurol Neurosurg Psychiatry	1999	67(3)	345-52
R22		Rougemont D	Local cerebral glucose utilisation in treated and untreated patients with Parkinson's disease	J Neurol Neurosurg Psychiatry	1984	47(8)	824-30
R23		Rousset O	3D simulations of radiotracer uptake in deep nuclei of human brain	Comput Med Imaging Braph	1993	17(4-5)	373-9
R24		Rudnicki SA	Nervous system dysfunction in Wwaldenstrom's macrogloubulinemia: response treatment	Neurology	1998	51(4)	1210-3
R25		Ruottinen H	Effects of MSO-B inhibition and peripheral COMT inhibition on fluorodopa PET in Parkinson's disease	Eur J Neurol	1995	2	161-
R26	(B29)	Ruottinen HM	Striatal 6-[18F]fluorodopa accumulation after combined inhibition of peripheral catechol-O-methyltransferase and monoamine oxidase type B: differing response in relation to presynaptic dopaminergic dysfunction	Synapse	1997	27(4)	336-46
R27		Ruottinen HM	[18F]fluorodopa PET shows striatal dopaminergic dysfunction in juvenile normal ceroid liposuscinosis	J Neurol Neurosurg Psychiatry	1997	6296)	622-5
R28	36	Ruottinen HM	Striatal [18F] fluorodopa utilization after COMT inhibition with entacapo studied with PET in advanced Parkinson's disease	J Neural Transm Park Dis Dement Sect	1995	10(2-3)	91-106

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S1		Saha GB	Radiopharmaceuticals for brain imaging	Semin Nucl Med	1994	44(9)	1622-8
S2	8 [ICP 31]	Sawle GV	Separating Parkinson's disease from normality. Discriminant function analysis of fluorodopa F 18 positron emission tomography data	Arch Neurol	1994	51(3)	237-43
S3		Sawle GV	The effect of entacapone (OR-611) on brain [18F]-6-L-fluorodopa metabolism implications for levodopa therapy of Parkinson's disease	Neurology	1994	44(7)	1292-7
S4		Sawle GV	Dopa-responsive dystonia	Ann Neurol	1994	36(5)	765-70
S5		Sawle GV	Asymmetrical pre-synaptic and post-synaptic changes in the striatal dopamine projection in dopa naive parkinsonism. Diagnostic implications the D2 receptor status	Brain	1993	116 (Pt 6)	853-67
S6		Sawle GV	[18F]-6-L-fluorodopa PET studies of graft and host dopaminergic function following fetal mesencephalic transplantation	Adv Neurol	1993	60	715-20
S7	10	Sawle GV	The detection of preclinical Parkinson's disease: what is the role of positron emission tomography	Mov Disord	1993	893)	271-7
S8		Sawle GV	Tansplantation of fetal dopamine neruons in Parkinson's disease: PET [18F]6-L-fluorodopa studies in two patients with putaminal implants	Ann Neurol	1992	31(2)	166-73
S9		Sawle GV	The rate of progression of Parkinson's disease	Ann Neurol	1992	31(2)	229
S10		Sawle GV	The identification of presymptomatic	Ann Neurol	1992	32(5)	609-17

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			parkinsonism: clinical and [18F]dopa positron emission tomography studies in an Irish kindred				
S11	[S11]	Sawle GV	Corticobasal degeneration. A unique pattern of regional cortical oxygen hypometabolism and striatal fluorodopa uptake demonstrated by positron emission tomography	Brain	1991	114 (Pt 1B)	541-56
S12		Sawle GV	Obsessional slowness functional studies with positron emission tomography	Brain	1991	114(5)	2191-2202
S13	[ICP 30]	Sawle GV	Striatal function in normal aging: implications for Parkinson's disease	Ann Neurol	1990	28(6)	799-804
S14	No # given	Scatton B	Dopamine deficiency in the cerebral cortex in Parkinson disease	Neurology	1982	32(9)	1039-40
S15		Schneider JS	Differential recovery of volitional motor function, lateralized cognitive function, dopamine agonist-induced rotation and dopaminergic parameters in monkeys made hemi-parkinsonian by intracarotid MPTP infusion	Brain Res (BIOA199598180310)			
S16		Schwarz J	Reduced striatal dopaminergic innervation shown by IPT and SPECT in patients under neuroleptic treatment: need for levodopa therapy?	Psychiatry Res	1998	83(1)	23-8
S17		Seeman P	Dopamine receptros and transporters in Parkinson's disease and schizophrenia	FASEB J	1990	4(10)	2737-44
S18		Shinotoh H	Fluorodopa and raclopride PET analysis of patients with Machado-Joseph disease	Neurology	1997	49(4)	1133-6
S19		Shinotoh H	Presynaptic and postsynaptic striatal	Neurology	1997	48(4)	1053-56

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			dopaminergic function in patients with manganese intoxication: A positron emission tomography study				
S20		Shinotoh H	[Neurotransmistter systems in the human brain studied by positron emission tomography].	Rinsho Shinkeigaku	1996	36(12)	1313-5
S21	[S21]	Shinotoh H	The use of PET in Parkinson's disease	Brain Cogn	1995	28(3)	297-310
S22		Shinotoh H	Dopamine D1 and D2 receptors in Parkinson's disease and striatonigral degeneration determined by PET	Adv Neurol	1993	60	488-93
S23		Shoulson J	Where do we stand on neuroprotection? Where do we go from here?	Mov Disord	1998	13 Supl 1	46-8
S24	68	Shulman LM	Levodopa toxicity in Parkinson disease: reality or myth?	Arch Neurol	2000	57	406-7
S25		Silber E	Hemiparkinsonism-hemiatrophy: A fluorodopa SPET study and beneficial response to medial pallidotomy	Neurology	1999	52 (6 Suppl 2)	A406-7
S26		Sjoholm H	Nigro-striatal degeneration demonstrated in parkinsonian patients with iodine-123-beta CIT SPECT: methods of quantitation	Acta Neurol Scand	1997	96(2)	91-6
S27		Smith GS	Serotonergic modulation of dopamine measured with [11c]raclopride and PET in normal human subjects	Am j Psychiatry	1997	154(4)	490-6
S28	[S28]	Snow BJ	Fluorodopa PET scanning in Parkinson's disease	Adv Neurol	1996	69	449-57
S29		Snow BJ	An aging effect in striatal fluorodopa uptake? Large versus small ROIs	J Cereb Blood Flow Metab	1994	14(5)	882-3
S30		Snow BJ	Positron emission tomographic studies of	Ann Neurol	1993	34(5)	733-8

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			dopa-responsive dystonia and early-onset idiopathic parkinsonism				
S31	[ICP 32]	Snow BJ	Human positron emission tomographic [18F]fluorodopa studies correlat with dopamine cell counts and levels	Ann Neurol	1993	3493)	324-30
S32	[S32]	Snow BJ	Positron emission tomography in Parkinson's disease	Can J Neurol Sci	1992	19 (1 Suppl)	138-41
S33		Snow BJ	The nigrostriatal dopaminergic pathway in Wilson's disease studied with positron emission tomography	J Neurol Neurosurg Psychiatry	1991	54(1)	12-7
S34		Snow BJ	Positron emission tomographic scanning demonstrates a presynaptic dopaminergic lesion in Lytico-Bodig. The amyotrophic lateral sclerosis-parkinsonism-dementia complex of Guam	Arch Neurol	1990	47(8)	870-4
S35	[S35]	Sossi V	Basal ganglia studies with 3D acquisition and 2D reconstruction on a retractable septa PET scanner	J Comput Assisted Tomogr	1994	18(6)	1004-9
S36		Sossi V	Recovery of the human striatal signal in a slice oriented positron emission tomograph	J Nucl Med	1993	34(3)	481-7
S37		Spencer DD	Unilateral transplantation of human fetal mesencephalic tissue into the caudate nucleus of patients with Parkinson's disease	N Engl J Med	1992	327(22)	1541-8
S38		Spencer SE	Altered pharmacokinetics of L-dopa metabolism in rat striatum deprived of dopaminergic innervation	Neurology	1984	34(8)	1105-8
S39		Stern Y	Cognitive change following MPTP exposure	Neurology	1990	40(2)	261-4
S40		Stocklin GL	Is there a future for clinical fluorine-18	Eur J Nucl Med	1998	25(12)	1612-6

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			radiopharmceuticals (excluding FDG)?				
S41	(B31)	Stout DB	Effects of large neutral amino acid concentrations on 6-[F-18]Fluoro-L-DOPA kinetics	J Cereb Blood Flow Metab	1998	18(1)	43-51
S42		Subramanian	Polymer-encapsulated PC-12 cells demonstrate high-affinity uptake of dopamine in vitro and 18F-Dopa uptake and metabolism after intracerebral implantation in nonhuman primates	Cell Transplant	1997	6(5)	469-77
T1		Takahashi H	Biochemical and fluorodopa positron emission tomographic findings in an asymptomatic carrier of the gene for dopa-responsive dystonia.	Ann Neurol	1994	35(3)	354-6
T3	4	Takahashi H	Evidence for a dopaminergic deficit in sporatdic amyotrophic lateral sclerosis on positron emission scanning	Lancet	1993	342 (8878)	1016-8
T2		Takahashi H	Clinical heterogeneity of dopa-responsive dystonia: PET observations	Adv Neurol	1993	60	586-90
T4	(C1)	Takikawa S	Input functions for 6-[fluorine-18]fluorodopa quantitaiton in parkinsonism: comparative studies and clinical correlations	J Nucl Med	1994	35(6)	955-63
T5		Taniwaki T	Positron emission tomography (PET) in Machado-Joseph disease	J Neurol Sci	1997	145(1)	63-7
T6		Taniwaki T	Positron emission tomography (PET) in 'pure akinesia'	J Neurol Sci	1992	107(1)	34-9
T7		Tanji H	PET study of striatal fluorodopa uptake and dopamine D2 receptor binding in a patient with juvenile parkinsonism	Eur J Neurol (BIOA1998003 22192)			

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T8		Tedroff J	Effects of the substituted (S)-3-phenylpiperidine (-)-OSU6162 on PET measurements in subhuman primates: evidence for tone-dependent normalization of striatal dopaminergic activity	Synapse	1998	28(4)	280-7
T9		Tedroff J	L-DOPA modulates striatal dopaminergic function in vivo: evidence from PET inveistgations in nonhuman primates	Synapse	1997	25(1)	56-61
T10		Tedroff J	Functional positron emission tomographic studies of striatal dopaminergic activity. Changes induced by drugs and nigrostiratal degeneration	Adv Neurol	1996	69	443-8
T11		Tedroff J	Levodopa-induced changes in synaptic dopamine in patients with Parkinson's disease as measured by [11C]raclopride displacement and PET.	Neurology	1996	4695)	1430-6
T12		Tedroff J	Cerebral uptake and utilization of therapeutic [beta-11C]-L-DOPA in Parkinson's disease measured by positron emission tomography.	Acta Neurol Scand	1992	85(2)	95-102
T13		Tedroff J	Estimation of regional cerebral utilization of [1C]-L-3,4-dihydroxy-phenylalanine (DOPA) in Tthe primate by positron emission tomography	Acta Neurol Scand	1992	85(3)	166-73
T14		Tedroff J	Central action of benserazide after COMT inhibition demonstrated in vivo by PET	J Neural Transm Gen Sect	1991	85(1)	11-7
T15		Tedroff J	Striatal kinetics of [11C]-(+)-nomifensine and 6-[18F]fluoro-L-dopa in Parkinson's disease	Acta Neurol Scan	1990	81(1)	24-30

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			measured with positron emission tomograph				
T16		Tedroff J	Monoamine re-uptake sites in the human evaluated in vivo by means of 11C-nomifesine and positron emission tomography: the effects of age and Parkinson's disease	Acta Neurol Scand	1988	77(3)	192-201
T17		Tetrud JW	Parkinsonism caused by petroleum waste ingestion	Neurology (BIOA199497407239)			
T18		Tewson TJ	PET radiopharmaceuticals: State-of-the-art and future prospects	Semin Nucl Med	1998	28(3)	221-34
T19		Tiihonen J	Striatal presynpatic dopamine function in type 1 alcoholics measured with positron emission tomography	Mol Psychiatry	1998	3(2)	156-61
T20	(C3)	Tissingh G	Nigrostriatal dopaminergic with iodine-123-beta CIT-FP/SPECT and fluorine-18-FDOPA/PET	J Nucl Med	1997	38(8)	1271-2
T21		Tissingh G	[123I]beta-CIT single-photon emission tomography in Parkinson's disease reveals a smaller decline in dopamine transporters with age than in controls	Eur J Nucl Med	1997	24(9)	1171-4
T22		Torstenson R	Effect of apomorphine infusion on dopamine synthesis rate relates to dopaminergic tone	Neuropharmacology	1998	37(8)	989-95
T23	6	Trebossen R	Validation of the three-dimensional acquisition mode in positron emission tomography for the quantitation of [18F]fluoro-DOPA uptake in the human striata	J Cereb Blood Flow Metab	1998	18(9)	951-9

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T24	26 (C4)	Trenkwalder C	Positron emission tomographic studies in restless legs syndrome	Mov Disord	1999	14(1)	141-5
T25		Turjanski N	Striatal dopaminergic function in restless legs syndrome: 18F-dopa and 11C-raclopride PET studies	Neurology	1999	52(5)	932-7
T26		Turjanski N	Dopaminergic function in patients with posttraumatic parkinsonism: an 18F-dopa PET study	Neurology	1997	49(1)	183-9
T27		Turjanski n	In vivo studies on striatal dopamine D1 and D2 site binding in L-dopa-treated Parkinson's disease patients with and without dyskinesias	Neurology	1997	49(3)	717-23
T28		Turjanski N	PET studies of the presynaptic and postsynaptic dopaminergic system in Tourette's syndrome	J Neurol Neurosurg Psychiatry	1994	57(6)	688-92
T29		Turjanski N	Comparison of striatal 18F-dopa uptake in adult-onset dystonia-parkinsonism, Parkinson's disease, and dopa-responsive dystonia	Neurology	1993	43(8)	1563-8
U1		Uitti RJ	Parkinsonism induced by solvent abuse	Ann Neurol	1994	35(5)	616-9
V1		Vallabhajosula S	PET studies in psychiatry: Validity, accuracy and future	J Nucl Med	1994	3591)	24-6
V2	5	Vidailhet M	Dopaminergic dysfunction in midbrain dystonia: anatomoclinical study using 3-dimensional magnetic resonance imaging and fluorodopa F 18 positron emission tomography	Arch Neurol	1999	56(8)	982-9
V3		Vingerhoets FJ	Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion?	Ann Neurol	1997	41(1)	58-64

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V4	[V4]	Vingerhoets FJ	Reproducibility and discriminating ability of fluorine-18-6-fluoro-L-Dopa PET in Parkinson's disease	J Nucl Med	1996	37(3)	421-6
V5		Vingerhoets FJ	Reproducibility of fluorine-18-6-fluorodopa positron emission tomography in normal human subjects	J Nucl Med	1994	35(1)	18-24
V6	[ICP 34]	Vingerhoets FJ	Longitudinal fluorodopa positron emission tomographic studies of the evolution of idiopathic parkinsonism	Ann Neurol	1994	36(5)	759-64
V7		Vingerhoets FJ	Positron emission tomographic evidence for progression of human MPTP-induced dopaminergic lesions	Ann Neurol	1994	3695)	765-70
V8	[ICP 35]	Volkow ND	PET evaluation of the dopamine system of the human brain	J Nucl Med	1996	37(7)	1242-56
W1		Wahl L	Quantification of dopamine metabolism in man: a mathematically justifiable approach	Phys Med Biol	1996	41(6)	963-78
W2		Wahl L	Modeling of fluorine-18-6-fluoro-L-Dopa in humans	J Nucl Med	1996	37(3)	432-7
W3	32	Wahl LM	Statistical power analysis for PET studies in humans	J Nucl Med	1998	39(10)	1826-9
W4		Wang RF	Determination of unchaged [18F]dopamine in human and non-human primate plasma during positron emission tomography studies: a new solid-phase extraction method comparable to radio-thin-layer chromatography analysis	J Chromatogr B Biomed Sci App	1997	693(2)	265-70
W5		Waters CH	Phenotypic expression of X-linked dystonia-parkinsonism (lubag) in two women	Neurology	1993	43(8)	1555-8
W6		Wayne MWR	Assessment of fetal tissue transplantation in	Neurology	1994	44(10)	1777-80

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			Parkinson's disease: Does PET play a role?				
W7		Weder BJ	Impaired somatosensory discrimination of shape	Hum Brain Mapp	1999	8(1)	1-12
W8	69	Weiner WJ	Is levodopa toxic?	Arch Neurol	2000	57	408-9
W9		Wenning GK	Short- and long-term survival and function of unilateral intrastiratal dopaminergic grafts in Parkinson's disease	Ann Neurol	1997	42(1)	95-107
W10		Westermark K	Neurological Wilson's disease studied with magnetic resonance imaging and with positron emission tomography using dopaminergic markers	Mov Disord	1995	10(5)	596-603
W11		Widner H	Bilateral fetal mesencephalic grafting in two patients with parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	N Engl J Med	1992	327(22)	1556-63
W12		Wolters EC	Dopamine agonists in Parkinson's disease	Neurology	1995	45 3 supl3	S28-34
W13	68	Wszolek ZK	Western Nebraska family (family D) with autosomal dominant parkinsonism	Neurology	1995	45(3)	502-5
W14		Wu JC	Decreasing striatal 6-FDOPA uptake with increasing duration of cocaine withdrawal	Neuropsychopharmacology	1997	17(6)	402-9
W15	(C7)	Wu JC	Increased dopamine activity associated with stuttering	Neuroreport	1997	8(3)	767-70
Y1	31	Yahr MD	Parkinson's disease: new approaches to diagnosis and treatment	Acta Neurol Scand Suppl	1993	146	22-5
Y2		Yahr MD	Parkinson's disease. The L-dopa era.	Adv Neurol	1993	60	11-7
Y3		Yee RE	Nigrostriatal reduction of aromatic L-amino acid decarboxylase activity in MPTP-treated squirrel monkeys: in-vivo and in-vitro	J Neurochem	1999	Revised manu-cript	1-39

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			investigations			W99-67	
Y4	[ICP 37]	Yee RE	Novel observations with FDOPA-PET imaging after early nigrostriatal damage	Ann Neurol	(submitted 1999)		1-39
Y5		Yost Y	Synthesis and preliminary evaluation of (s)-(2-[18F]fluoro-4,5-dihydroxyphenyl)-2-methyl L-alanine, (S)-[18F]-FMEDOPA, a potentially improved imaging agent for the presynaptic dopmainergic nervous system	Nucl Med Biol	1996	2397)	857-65
Y6	(C10)	Yu DC	The assessment of the non-equilibrium effect in the 'patlak analysis' of Fdopa PET studies	Phys Med Biol	1995	40(7)	1243-54
Y7	(C9)	Yu DC	Methods for improving quantitation of putamen uptake constant of FDOPA in PET studies	J Nucl Med	1993	34(4)	679-88
Z1		Zigmond MJ	Partial damage to nigrostriatal bundle: compensatory changes and the action of L-dopa	J Neural Transm Suppl	1990	29	217-32
1	<PT>	Albanese A	Chronic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to monkeys: Behavioral, morphological and biochemical correlates.	Neuroscience	1993	55	823-32
2	<PK>	Begg CB	Assessment of diagnostic tests when disease verification is subject to selection bias	Biometrics	1983	39	207-15
3	<PK>	Bhargava HK	Beyond spreadsheets: tools for building decision support systems	Computer	1999	32	31-9
4	<PT>	Burns RS	A primate model of Parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantis nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.	Proc Natl Acad Sci	1983	80	4546-50
5	<PT>	Cantacuzene D	Effect of fluorine substitution on the agonist	Science	1979	204	1217-9

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			specificity of norepinephrine				
6	<PK>	Cedarbaum JM	Effect of supplemental carbidopa on bioavailability of L-dopa	Clin Neuropharmacol	1986	9(2)	153-9
7	<PK>	Collins JM	Positron emission tomography for selection and assessment of therapy				
8	<PT>	Cumming P	The metabolism of [18F]6-fluoro-L-3,4-dihydroxyphenylalanine in the hooded rat	J Neurochem	1987	48	601-8
9	<PK>	Devous MD	SPECT brain imaging in epilepsy: a meta-analysis	J Nucl Med	1998	39	285-93
10	<PK>	Firnau G	Metabolites of 6-[18F]fluoro-L-dopa in human blood	J Nucl Med	1988	29(3)	363-9
11	<PT>	Firnau G	Cerebral metabolism of 6-[18F]fluoro-L-3,4-dihydroxyphenylalanine in the primate	J Neurochem	1987	48	1077-82
12	<PT>	Garnett ES	Dopamine visualized in the basal ganglia of living man	Nature	1983	305	137-8
13	<PT>	Garnett S	Striatal dopamine metabolism in living monkeys examined by positron emission tomography	Brain Res	1983	280	169-71
14	<PK>	Hammerstad JP	The transport of L-6-fluorodopa and its metabolites from the blood to cerebrospinal fluid and brain	Ann Neurol	1993	34(4)	603-8
15	<PK>	Hartvig P	Regional brain kinetics of 6-fluoro-(beta-11C)-L-dopa and (beta-11C)-L-dopa following COMT inhibition. A study in vivo using positron emission tomography	J Neural Transm Gen Sect	1992	87(1)	15-22
16	<PT>	Hoffman JM	The effects of carbidopa administration on 6-[18F]fluoro-L-dopa kinetics in positron emission tomography	J Nucl Med	1992	33	1472-77
17	<PK>	Irwig L	Meta-analytic methods for diagnostic test accuracy	J Clin Epidemiol	1995	48	119-32
18	<PK>	Jeffrey RF	The effect of carbidopa and indomethacin on the	Br J Clin	1988	25(2)	195-201

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			renal response to gamma-L-glutamyl-L-dopa in normal man	Pharmacol			
19	<PK>	Kaplan RM	A general health policy model: update and applications	Health Serv Res	1988	23	203-35
20	<PK>	L'abbe KA	Meta-analysis in clinical research	Ann Intern Med	1987	107	224-33
21	<PT>	Langston JW	The next frontier in Parkinson's disease: Presymptomatic detection	Neurology	1991	41 (suppl 2)	5-7
22	<PT>	Langston JW	Chronic parkinsonism in humans due to a product of meperidine-analog synthesis	Science	1983	219	979-80
23	<PK>	Laruelle M	Imaging dopamine transmission in schizophrenia: a review and meta-analysis	Q J Nucl Med	1998	42	211-21
24	<PT>	Leenders KL	Inhibition of L-[18F]fluorodopa uptake into human brain by amino acids demonstrated by positron emission tomography	Ann Neurol	1986	20	258-62
25	<PK>	Leppert PS	The effects of carbidopa dose and time and route of administration on systemic L-dopa levels in rats	Pharm Res	1988	5(9)	587-91
26	<PT>	LeWitt PA	Markers of dopamine metabolism in Parkinson's disease	Neurology	1992	42	2111-17
27	<PK>	Littenberg B	Technetium bone scanning in the diagnosis of osteomyelitis: a meta-analysis of test performance. Diagnostic Technology Assessment Consortium	J Gen Intern Med	1992	7	158-64
28	<PT>	Lloyd KG	Occurrence and distribution of armatic L-amino acid (L-DOPA) decarboxylase in the human brain	J Neurochem	1972	19	959-67
29	<PT>	Luxen A	Production of 6-[18F]fluoro-L-dopa and its metabolism in vivo-a critical review	Nucl Med Biol	1992	19	149-58
30	<PK>	Lyytinen J	Simultaneous MAO-B and COMT inhibition in L-Dopa-treated patients with Parkinson's disease	Mov Disord	1997	12(4)	497-505
31	<PK>	Maguire RP	Variance in parametric images: direct estimation	Phys Med Biol	2000	45(1)	91-102

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			from parametric projections				
32	<PK>	Maguire RP	An investigation of multiple time/graphical analysis applied to projection data: theory and validation	J Comput Assist Tomogr	1997	21(2)	327-31
33	<PT>	Martin WRW	Nigrostriatal function in humans studied with PET	Ann Neurol	1989	26	535-42
34	<PK>	Missimer J	On two methods of statistical image analysis	Hum Brain Mapp	1999	8(4)	245-58
35	<PK>	Moses LE	Combining independent studies of a diagnostic test into a summary ROC curve: data-analytic approaches and some additional considerations	Stat Med	1993	12	1293-1316
36	<PK>	Mozley PD	Dosimetry of a D2/D3 dopamine receptor antagonist that can be used with PET or SPECT	J Nucl Med	1995	36(7)	1322-31
37	<PT>	Pate B	Correlation of striatal fluorodopa uptake in the MPTP monkeys with dopaminergic indices.	Ann Neurol	1993	34	331-8
38	<PK>	Pestana M	Reduced urinary excretion of dopamine and metabolites in chronic renal parenchymal disease	Kidney Blood Press Res	1998	21(1)	59-65
39	<PK>	Rose S	Peripheral pharmacokinetic handling and metabolism of L-dopa in the rat: the effect of route of administration and carbidopa pretreatment	J pharm Pharmacol	1991	43(5)	325-30
40	<PT>	Sawle GV	Transplantation of fetal dopamine neruons in Parkinson's disease: PET [18F]6-L-fluorodopa studies in two patients with putaminal implants	Ann Neurol	1992	31(2)	166-73
41	<PK>	Thacker SB	Meta-analysis. A quantitative approach to research integration	JAMA	1988	259	1685-89
42	<PT>	Torsten R	A comparison of 11C-labeled L-dopa and L-fluorodopa as PET tracers for presynaptic dopaminergic system	J Cereb Blood Flow Metab	1999	19	1142-9
43	<PK>	Torstenson R	A comparison of 11C-labeled L-DOPA and L-fluorodopa as positron emission tomography	J Cereb Blood Flow Metab	1999	19910)	1142-9

PET: F-DOPA LITERATURES
[MASTER INDEX]

Tab #	Origin	Primary Author	Title	Journal	Year Published	Volume	Pages
			tracers for the presynaptic dopaminergic system				
44	<PK>	Wahl L	The distribution and kinetics of [18F]6-fluoro-3-O-methyl-L-dopa in the human brain	J Cereb Blood Flow Metab	1994	14(4)	664-70
Book		Goodman and Gillman	Pharmacopeia		1996	9th edition	
Book		Samuel/Feske	Office Practice of Neurology		1996		
Book		Cooper	Biochemical Basis of Neuropharmacology		1996	7th edition	
Book		McGraw Hill	Neurology Principle and Practice		1997		
Book			Physician's Desk Reference		1999	53rd edition	
Book		Jankovic/ Tolosa	Parkinson's disease and movement disorder			3RD edition	991-1016
Book		Murray	Nuclear Medicine in clinical Diagnosis and Treatment		1994	Volume 1	589-643
Book		Harbert	Nuclear Medicine: Diagnosis and Therapy		1996		375-85
Review			The Safety and Efficacy of COMT Inhibitors (sumposium at XIII International Congress on Parkinson's Disease, Vancouver, Canada		2000	Supplement (April)	

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/s/

SALLY J HARGUS
06/10/2013

ADEBAYO A LANIYONU
06/10/2013

PHARMACOLOGY/TOXICOLOGY Memo for PreNDA 200655

NDA Number: 200655 **IND Number 78861** **Reviewer: Sally Hargus, Ph.D., DMIP**	**Applicant: Feinstein Institute, Thomas Chaly**	**Stamp Date:** **14 and 21 March 2012**
Drug Name: Fluorodopa F18 Injection	**Type: NDA** **505(b)(2); NME**	**Meeting Date:** **16 April 2012**

The sponsor of NDA 200655 submitted a PreNDA Meeting Package and Questions for FDA regarding this re-submission of [18F]FDOPA for PET detection of dopaminergic striatal (b) (4) in patients with suspected Parkinson's Disease (PD). The procedure is proposed as an adjunct test with other diagnostic evaluations.

The sponsor had previously submitted an NDA for the same product in 2010. The agency issued a Refuse-to-File letter, due to major deficiencies in the application, such as the complete absence of the nonclinical section and inadequate clinical and CMC information. Regarding the nonclinical deficiency, the Division recommended that the applicant provide Pharmacology and Toxicology information in the revised NDA. The recommendation was not related to a specific safety issue; rather, to provision of basic information on the pharmacological basis of the diagnostic agent and the nonclinical safety profile of FDOPA.

In the sponsor's current nonclinical section, appropriate reference was made to the July 28, 2000, Public Meeting between FDA and the PET community. The PET drug, Fluorodopa F18 Injection, was reviewed and discussed during the public meeting. At that time, FDA had deferred a decision on the approval of Fluorodopa F18 Injection to a later date (to be determined). The transcript of the meeting is available on the Worldwide Web at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm182855.htm.

Also during the 28 July 2000 Public Meeting, Dr. Adebayo Laniyonu presented an overview of Fluorodopa (FDOPA) and L-DOPA pharmacology and toxicology, based on his review of nonclinical literature available from the public domain. The Master List of articles reviewed and discussed at the meeting is available on the Worldwide Web at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm182855.htm.

In his written review, Dr. Laniyonu concluded that FDOPA is an acceptable metabolic tracer for dopaminergic activity, and that the need for typical pharmacology and toxicology studies in an application could be waived due to 1) extensive clinical experience without reports of safety related concerns; 2) similarity in the metabolism of LDOPA and FDOPA; 3) safety data base for LDOPA; and 4) low mass dose of FDOPA administered in PET studies (Dr. Adebayo Laniyonu, Review of Fluorodopa, July 2000). However, it was noted that various methodologies for producing Fluorodopa F18 Injection could result in varying profiles of degradants and impurities, which may need to be qualified for safety in some final products.

No specific nonclinical questions were submitted by the sponsor in the current Meeting Package. The nonclinical section was included in the current preNDA materials and should (or will) be a component of the NDA submission, I presume.

Reference ID: 3114275
Reference ID: 4514938

The sponsor included a draft label for the product. The label will be reviewed and evaluated during the NDA Review period.

The sponsor did not provide the maximum mass dose of FDOPA in the label or in the Meeting Materials. The sponsor will be requested to provide the mass dose of FDOPA contained in the product.

Comments for the sponsor:

1. Include the Nonclinical Pharmacology and Toxicology section in your NDA, as required under 21 CFR 314.50(d)(2). The nonclinical information, as stated in Section 4 of the preNDA submission (dated 14 March 2012), was acceptable for filing an NDA.

2. Include a statement of the maximum **mass** dose of [18F]FluoroDOPA to be administered to a patient undergoing the PET scan. The mass dose of drug substance should be stated in each major section of your NDA.

Reference ID: 3114275
Reference ID: 4514938

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/s/

SALLY J HARGUS
04/10/2012

ADEBAYO A LANIYONU
04/11/2012

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

ADDENDUM - Statistical Review and Evaluation

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 200-655 Resubmission Document Number 19, Re-submission with major amendment
Drug Name:	Flurodopa F 18 (FDOPA) injection - PET Imaging drug
Indication(s):	Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes (PS). Fluorodopa F 18 PET is an adjunct to other diagnostic (b) (4)
Applicant:	Feinstein Institute medical Research via Thomas Chaly, Ph.D.
Date(s):	NDA Submission: December 15, 2015 PDUFA Date: September 15, 2016
Review Priority:	Class 2 resubmission with major amendment
Biometrics Division:	OB/DBV
Statistical Reviewer:	Satish Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Secondary Reviewer Thomas E. Gwise, Ph. D., Deputy Director Division of Biostatistics V
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Brenda Ye, M. D. Clinical TL/DD: Alex Gorovets, M. D. / Louis Marzella, M. D.
Project Manager:	Thuy Nguyen

Keywords: Expanded Access IND, Positive percent agreement, Negative percent agreement, Sensitivity, Specificity

Reference ID: 3964194

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1. EXECUTIVE SUMMARY

This is an addendum to the primary statistical report (dated 04/26/2016) of NDA 200655 for Fluorodopa F 18 (FDOPA) resubmission. In response to FDA's Complete Response letter given to the applicant in 2013, the sponsor submitted the results from a new clinical trial (#17) that the applicant conducted.

The safety and efficacy of FDOPA (short-lived radiopharmaceutical used in Positron Emission Tomography (PET)) were evaluated in one single-center, single-arm study (Study #17): 51 subjects were screened, 45 adult subjects with suspected parkinsonian syndromes (PS) were enrolled, and completed the study.

A literature search and written reviews for F-DOPA as part of developing approval procedures under Section 121 of 1997 FDA Modernization Act (FDAMA) was performed the year 2000 by the FDA imaging team. The reports concluded that the metabolic pathways for endogenous dopamine, the therapeutic drug LDOPA and FDOPA are "qualitatively" similar, and it is therefore reasonable to infer that the human body will also "handle" FDOPA similarly. FDOPA may be considered as a "**functional biomarker**" of the presynaptic dopaminergic system in normal subjects and in patients with movement disorders such as PD. The report also pointed out several limitations.

The SGE1 agreed with the sponsor image interpretation for 41/45 (91%) subjects. The SGE1 further stated that images were relatively easy to read and that he does not know of any disadvantages compared to the currently marketed US imaging drug.

The SGE2 preferred to read the black-and-white images and agreed with the sponsor image interpretation for 42/45 (93%) subjects. He further stated that there are some advantages with FDOPA compared to the currently marketed US imaging drug, such as: shorter uptake, no need for thyroid blocking, better resolution, lower radiation dose / less radiation exposure and less limitation of other drug used.

These 45 patients were followed-up for up to 2 years by the same referring physician for the final diagnosis. The physician also had knowledge of the F-DOPA scan results. This follow-up clinical diagnosis is available in 36 out of 45 patients. Out of 36, there were 31 positive PET scans and 5 negative PET scans. The remaining 9 subjects did not return for the follow-up evaluation. These 9 patients were all negative PET scans. The sponsor has called the results of these evaluations at the follow-up as standard of truth (SOT). The truth standard was the diagnosis done by the referring physician which also included access to the FDOPA imaging results. This fact renders the data difficult to interpret.

In this report, evaluations at the follow-up visit are considered a reference standard for visualization, not truth standard for PS disease. In this report, FDOPA image outcomes were compared to a reference clinical diagnostic standard of "PS" or "non-PS". 31 patients (86%) were diagnosed positive (+) for PD; 5 (14%) were diagnosed negative (-) at the 2nd visit by the same neurologist who was the referring physician. .

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Table 1 below shows the appropriate visualization parameters, positive percent agreement and negative percent agreement of the FDOPA image results with the reference clinical diagnostic standard, defined as follows:

Positive percent agreement represents the percent of patients with abnormal (positive) FDOPA images among all the patients with a clinical diagnostic reference standard of PS. The sample size for this agreement measure in this study is 31. (The sponsor has called it Sensitivity).

The negative percent agreement represents the percent of patients with normal (negative) FDOPA images among the patients with a non-PS clinical diagnostic reference standard. The sample size for this agreement measure in this study is 5. (The sponsor has called it Specificity).

Table 1: Positive and Negative Percent Agreements with follow-up evaluation for Study# 17

	Positive percent agreement (% patients with an abnormal FDOPA image among patients with PS, N=31) and 95% Exact Confidence Interval	Negative percent agreement (% patients with a normal FDOPA image among patients with non-PS, N=5) and 95% Exact Confidence Interval
Reader 1	29/31=94% (79 , 99)	5/5=100% (48 , 100)
Reader 2	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
Reader 3	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
NDA Reads	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
SGE1 reads	27/31=87% (70 , 96)	4/5=80% (28 , 99)
SGE2 reads (B & W)	29/31=94% (79 , 99)	4/5=80% (28 , 99)
SGE2 reads (Color)	30/31=97% (83 , 99.8)	3/5=60% (15 , 93)

All the reads for positive percent agreement are in the same direction. However for the negative percent agreement, the sample is too small to draw any conclusion.

The SGE findings does not impact the findings already documented in the statistical reviews. The data provided for negative agreement are not adequate to draw any conclusions due to very small sample size.

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2. INTRODUCTION

2.1 Background

The safety and efficacy of FDOPA (short-lived radiopharmaceutical used in Positron Emission Tomography (PET)) were evaluated in one single-center, single-arm study (Study #17): 51 subjects were screened, 45 adult subjects with suspected parkinsonian syndromes (PS) were enrolled, and completed the study. There were 3 blinded independent readers. The sponsor stated that no reader training or instructions were provided and it was based on the experience of independent- blinded read by (2) neurologist and (1) physicist.

All three readers appeared to be qualified (based on experience) and interpreted the images independently. Suggestive evidence of any collaborative image interpretation was not observed. The standard of truth diagnosis was established by a neurologist based on clinical follow up (clinical response to treatment), typically the original referring physician who did not otherwise participate in the study.

This resubmission of NDA 200655 for Fluorodopa F 18 (FDOPA) consists of a response to FDA's Complete Response letter given to the applicant in 2013, in terms of submission of results from a new clinical trial (#17) that the applicant conducted. Details of previous communications between the applicant and FDA as well as the information about this drug can be found in the primary statistical review.

The safety and efficacy of FDOPA (short-lived radiopharmaceutical used in Positron Emission Tomography (PET)) were evaluated in one single-center, single-arm study (Study #17), For *Study 17:* 51 adult subjects were screened, 45 subjects with suspected **Parkinsonian Syndromes (PS)** were enrolled, and 45 completed the study. These 45 patients were studied under an IND expanded access protocol. There was no patient selection process, no consecutive patients or healthy volunteers. The patients were referred for imaging because the diagnosis was unclear and the patient was given a dose of carbidopa before the scan to improve image quality. The sponsor stated that no reader training or instructions were provided and it was based on the experience of independent- blinded read by (2) neurologist and (1) physicist. These 45 patients were then clinically followed for up to two years for clinical outcome. Three independent readers interpreted the PET scans to evaluate the shape and size of the striatum. The primary imaging endpoint was either positive or negative for dopaminergic neuron loss. The Sponsor stated that any changes in size or shape would be considered significant (PS). The software program used by the Sponsor was not for imaging analysis interpretation, but rather for image display.

These 45 patients were followed-up for up to 2 years by the same referring physician for the final diagnosis. The physician also had knowledge of the F-DOPA scan results. This follow-up clinical diagnosis is available in 36 out of 45 patients. Out of 36, there were 31 positive PET scans and 5 negative PET scans. The remaining 9 subjects did not return for the follow-up evaluation. These 9 patients were all negative PET scans. The sponsor has called the results of these evaluations at the follow-up as standard of truth (SOT). The truth standard was the

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diagnosis done by the referring physician which also included access to the FDOPA imaging results. This fact renders the data difficult to interpret.

In this report, evaluations at the follow-up visit are considered a reference standard for visualization, not truth standard for PS disease. In this report, FDOPA image outcomes were compared to a reference clinical diagnostic standard of "PS" or "non-PS". 31 patients (86%) were diagnosed positive (+) for PD; 5 (14%) were diagnosed negative (-) at the 2nd visit by the same neurologist blinded to NDA readings.

The reference clinical diagnostic standard for "PS" consisted of the following diagnoses: Parkinson's disease (PD), Gait Freeze, Cortical Basal Ganglion Degeneration (CBD), Pisa Syndrome, multiple system atrophy (MSA), and progressive supra-nuclear palsy (PSP). The applicant considered that these conditions have been associated with the loss of dopaminergic neurons. FDOPA imaging was not designed to distinguish among the conditions. The reference clinical diagnostic standard for "non-PS", according to the applicant, consisted of an essential tremor (ET) diagnosis, or other non-PS diagnosis (Dopamine Responsive Dystonia (DRD), Subject without Evidence of Dopaminergic Deficit (SWEDD)). Sixty-five to 100 minutes after FDOPA administration by intravenous injection (150-185 MBq, 4.05-5.0 mCi), subjects underwent PET scan and attenuation correction.

The primary end point for this study was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." "Loss" of dopaminergic neurons in the striatum was based upon the reader's judgment of what a "no loss" image looks like, not upon a prior scan in the same patient.

2.2 Standard of Truth

The histopathological examination at autopsy is the gold standard in establishing the diagnosis of movement disorders including PD. Currently and historically, the next best tool to autopsy in establishing a diagnosis is the one made by a movement disorder specialist (a neurologist with additional specialized training in movement disorders). It is the belief of some that the diagnosis of PD particularly in its early stages may be difficult to make.

David J. Brooks stated in an article – "Imaging Approaches to Parkinson Disease" (Imperial College, London, April 2010; Journal of Nuclear Medicine)

"The definitive diagnosis of idiopathic Parkinson disease (PD) requires histologic demonstration of intraneuronal Lewy body inclusions in the substantia nigra compacta, and such demonstration is clearly impractical during life….Clinicopathologic studies suggest that when established PD is diagnosed according to current U.K. Brain Bank criteria, there is a 90% concordance between expert clinical impression and the presence of nigral Lewy bodies.

In early PD, however, the full triad of clinical symptoms and signs (rest tremor, bradykinesia, and rigidity) may not yet be manifested. Differential diagnoses include benign essential or dystonic tremors and parkinsonism associated with exogenous agents such as dopamine receptor–blocking drugs. These conditions are not associated with nigral degeneration or striatal dopamine deficiency. In up to 15% of cases labeled as early PD by investigators, imaging has shown normal dopamine terminal function suggestive of an alternative diagnosis. Given this

statistic, the ability to noninvasively detect altered nigral structure or striatal dopamine terminal function potentially provides valuable tools that can help increase diagnostic specificity for dopamine-deficient parkinsonian syndromes and rationalize management decisions at initial stages of disease."

2.3 A Summary of FDA Review of F-DOPA in the year 2000

A literature search and written reviews for F-DOPA as part of developing approval procedures under Section 121 of 1997 FDA Modernization Act (FDAMA) was performed the year 2000. The included:

- Pharmacology/Toxicology – Adebayo Laniyonu, Ph.D.
- Biopharmaceutics – Alfredo Sancho, Ph.D.
- Clinical- Ramesh Raman, M.D.

The review technically began in winter of 1999 and the findings were presented in the public meeting of July 28, 2000. A summary of the conclusions cited by the team based on extensive literature search in the year 2000 is given below:

- The metabolic pathways for endogenous dopamine, the therapeutic drug LDOPA and FDOPA are "qualitatively" similar, and it is therefore reasonable to infer that the human body will also "handle" FDOPA similarly.

- Alteration in the DA system (amongst others) due to neurodegeneration is the pathophysiological hallmark of movement disorders, including PD. PET imaging with FDOPA, based on the known mechanism of action, reflects the status of the dopaminergic system and, therefore, any alteration in its uptake reflects an abnormality in this system.

- It is suffice to summarize that FDOPA targets the presynaptic dopaminergic sites in diseases such as PD. The extent of the correlation between imaging and pathology in movement disorders such as PD, is questionable due to methodological and technological limitations.

- Based on the search and the literature data, the clinical report concluded that the mechanism of action of FDOPA-PET, in that it targets the dopaminergic system can be established. In this context, FDOPA may be considered as a "**functional biomarker**" of the presynaptic dopaminergic system in normal subjects and in patients with movement disorders such as PD. The clinical meaning of these alterations (either between normal verses abnormal or within abnormal) has not been established.

- Although there were no data that could be considered for efficacy approval, the scientific information so generated from this database was found to be helpful in the

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understanding of FDOPA-PET from a global perspective, i.e., in research setting and in clinical investigations. This scientific information may be regarded as a foundation upon which further clinical studies may be based.

- **Issues and Limitations on Methodology, Technology & Image Analyses**

  There are technology and methodology concerns that are generally related to the PET imaging. These are "innate" to most of the agents that use PET. These are applicable to FDOPA-PET and they do play a role in these assessments as they affect several of the findings. Some of the important issues/concerns related to the techniques are:

  1. Reproducibility
  2. The Analysis of FDOPA-PET data- Methodological Issues
  3. Instrumentation Related- Technological Issues
  4. Image Interpretation Issues- ROI approach, Partial Volume Effects, Qualitative v/s Quantitative Reads
  5. Effects of Drugs (AAAD inhibitor, COMT inhibitor)

The findings from the literature are at best "hypotheses" generating and the articles/ studies cannot be pooled in a fashion that can be validated for a claim. The assessment of "lack of robustness" in the existing scientific literature is independent of the concerns on the methodology or technology that was used. As mentioned above, none of the articles met the required criteria that rendered them adequate enough that the data could be validated. Although these articles are contributory in providing valuable scientific information, the existing data is not robust, per se, in achieving a claim.

2.4 Comments by FDA Inspection Team

"The single pivotal study for this NDA was audited at good clinical practice (**GCP**) inspection of the sponsor-clinical investigator site. No significant GCP deficiencies were observed and a Form FDA 483 was not issued. All three readers appeared to be qualified (based on experience) and interpreted the images independently. Suggestive evidence of any collaborative image interpretation was not observed. The standard of truth diagnosis was established by a neurologist based on clinical follow up (clinical response to treatment), typically the original referring physician who did not otherwise participate in the study.

The overall study conduct appeared GCP-compliant, including oversight of study conduct. All audited data were adequately verifiable against source records and case report forms (**CRFs**). The data from the inspected site appear reliable as reported in the NDA."

2.5 Comments by SGE1 Dr. Henry D. Royal, M.D., June 27, 2016

In a teleconference meeting held on Monday, June 27, 2016 with SGE 1 Dr. Henry D. Royal, M.D., Mallinckrodt Institute of Radiology regarding **[F-18] Fluorodopa (FDOPA) Injection to discuss the FDA Divisional Assignment dated May 31, 2016 of the PET images, the SGE1 made the following points:**

(1) SGE1 stated that the images for Patient # (b) (6) were not ideal to read because the target to background contrast was decreased.

(2) SGE1 stated that the images were relatively easy to read. Regarding the proposed labeling, Section 2.8: Image Interpretation, the SGE stated those instructions are adequate and in practice, a standard work station would suffice and an image software program would not be necessary.

(3) The SGE1 disagreed with the Sponsor image interpretations for the following:

i) Patient # (b) (6): SGE interpretation – Normal. Sponsor interpretation – Abnormal.

ii) Patient # (b) (6): SGE interpretation – Abnormal (because black and white images differed from the color images). Sponsor interpretation - Normal. SGE further stated regarding patient # (b) (6) that he had a hard time convincing himself that the black-and-white (BW) images that were provided matched the color images. He said that he would just ask the submitter to confirm that the BW and color images for Patient / Case (b) (6) are correct.

However, the SGE1 agreed with the Sponsor image interpretations for the other patients.

(4) The SGE1 stated he does not know of any disadvantages compared to the currently marketed US imaging drug.

2.6 Comments by SGE2 Dr., Peter Herscovitch, M.D., NIH, July 11, 2016

(1) The SGE2 preferred to read the black-and-white images rather than the color images.

(2) The SGE2 stated a few images had higher background which was not ideal to read because the scan intensity was scaled to the maximum.

(3) The SGE2 stated that the images were relatively easy to read.

(4) The SGE2 agreed with most of the Sponsor image interpretations and disagreed with 3 out of the 45 black-and-white images.

(5) The SGE2 stated there are some advantages with FDOPA compared to the currently marketed US imaging drug, such as:

i) shorter uptake
ii) no need for thyroid blocking
iii) better resolution
iv) lower radiation dose / less radiation exposure and
v) less limitation of other drug used.

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3. STATISTICAL EVALUATION

The safety and efficacy of FDOPA (short-lived radiopharmaceutical used in Positron Emission Tomography (PET)) were evaluated in one single-center, single-arm study (Study #17), For *Study 17:* 51 adult subjects were screened, 45 subjects with suspected **Parkinsonian Syndromes (PS)** were enrolled, and 45 completed the study. These 45 patients were studied under an IND expanded access protocol.

(b) (6) At the onset of PD and related diseases, the patients will have a loss of dopaminergic neurons in the range of 45 to 50%. This loss will be reflected in the PET scan based on the reduced uptake of Fluorodopa F 18 in the striatum. Patients with Parkinson's or related disease (Parkinsonism) will indicate a loss of dopaminergic neurons in the striatum depending upon the severity of the disease (a reduced uptake of Fluorodopa F 18 in the putamen or putamen and caudate unilaterally or bilaterally with the loss of dopaminergic neurons). Patients with essential tremor will have no dopaminergic neuronal loss and the PET scans will be normal. (b) (6) . Patients with confirmed Parkinson's disease are treated differently from patients with essential tremor. Therefore, a differential diagnosis for patients with parkinsonian syndromes is essential for the proper management of these two diseases.

Among the 45 patients in Study # 17, 29% (13/45) were female and the average age was 58.6 years (standard deviation = 13.1). The baseline clinical diagnoses consisted of: probable PD, possible PD, possible ET, and other diagnoses. In this study, FDOPA image outcomes were compared to a reference clinical diagnostic standard of "PS" or "non-PS".

The primary end point for this study was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." "Loss" of dopaminergic neurons in the striatum was based upon the reader's judgment of what a "no loss" image looks like, not upon a prior scan in the same patient.

There were three blinded independent readers. The sponsor stated that no reader training or instructions were provided and it was based on the experience of independent- blinded read by (2) neurologist and (1) physicist. **FDA Inspection Team** stated that "all three readers appeared to be qualified (based on experience) and interpreted the images independently. Suggestive evidence of any collaborative image interpretation was not observed. The standard of truth diagnosis was established by a neurologist based on clinical follow up (clinical response to treatment), typically the original referring physician who did not otherwise participate in the study. Overall, study conduct appeared to be adequately consistent with the study description presented in the NDA. All audited data were adequately verifiable against source records and CRFs. The data from this CI site appear reliable as reported in the NDA."

Table 2 provides Reader's Evaluation, NDA Reading, SGE Reading and & Follow-up Evaluation

Reference ID: 3964194

Table 2: Reader's Evaluation, NDA Reading, SGE Reading and & Follow-up Evaluation

Sub. ID #	Readers #			NDA Reading	SGE1 Reading	SGE2 Reading B&W	SGE2 Reading Color	2nd Visit Follow-up DX	Months to follow-up 2nd visit
	1	2	3						
(b) (4)									

"+" PS "-" no PS. Disagreements by the SGEs are highlighted.

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n = 45 (Subject # (b) (6) -- no scan)
36 patients were followed up (second visit to the same neurologist)
31 patients were diagnosed positive for PD; 5 negative and remaining 9 did not return for 2nd visit in spite of repeated telephone calls and efforts
Subject # (b) (6) had a final diagnosis of iMSA (Parkinsonism vs. preautonomic failure). It could be classifies as both PS (+) or no PS (-). Results presented are for PS (+) corresponding to DOPA loss for both Freezing Gait and MSA

Mean follow-up months = 12.3 SD = 6.1 Range -- 0.25 months to 26 months;
Median time to follow-up months = 13 months;
Inter Quartile Range -- 10 months to 15.75 months

Agreement (45 scans)

There were three (3) three independent blinded PET scan readers and were also blinded to the clinical information and physicians' diagnosis.

All 3 readers agreed on 44 out of 45 scans (98%).

Two (2) out of 3 readers agreed on all 45 out of 45 scans (100%). This reading was termed as NDA reading.

In the original submission study # 15/16 -, there was no variability among three scan readers with regards to the visual assessment of the PET scans.

SGE1 agreed with 41 out of 45 NDA readings (91%)
SGE2 agreed with 42 out of 45 NDA readings (93%) while reading B&W images
SGE2 agreed with 40 out of 45 NDA readings (89%) while reading color images

Agreement with Neurologist at the second visit follow-up

36 patients were followed up (second visit to the same neurologist)

31 patients (86%) were diagnosed positive (+) for PD; 5 (14%) were diagnosed negative (-) at the 2nd visit by the same neurologist blinded to NDA readings.

Table below shows the appropriate visualization parameters, positive percent agreement and negative percent agreement of the FDOPA image results with the reference clinical diagnostic standard, defined as follows

Positive percent agreement represents the percent of patients with abnormal (positive) FDOPA images among all the patients with a clinical diagnostic reference standard of PS. The sample size for this agreement measure in this study is 31. The sponsor has called it Sensitivity.

The negative percent agreement represents the percent of patients with normal (negative) FDOPA images among the patients with a non-PS clinical diagnostic reference standard. The

Reference ID: 3964194

sample size for this agreement measure in this study is 5, which is too small to draw any conclusions. The sponsor has called it Specificity.

Table 3: Positive and Negative Percent Agreements with follow-up evaluation for Study# 17

	Positive percent agreement (% patients with an abnormal FDOPA image among patients with PS, N=31) and 95% Exact Confidence Interval	Negative percent agreement (% patients with a normal FDOPA image among patients with non-PS, N=5) and 95% Exact Confidence Interval
Reader 1	29/31=94% (79 , 99)	5/5=100% (48 , 100)
Reader 2	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
Reader 3	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
NDA Reads	30/31=97% (83 , 99.8)	5/5=100% (48 , 100)
SGE1 reads	27/31=87% (70 , 96)	4/5=80% (28 , 99)
SGE2 reads (B & W)	29/31=94% (79 , 99)	4/5=80% (28 , 99)
SGE2 reads (Color)	30/31=97% (83 , 99.8)	3/5=60% (15 , 93)

All the reads for positive percent agreement are in the same direction. However for the negative percent agreement, the sample is too small to draw any conclusion.

The SGE findings does not impact the findings already documented in the statistical reviews. The data provided for negative agreement are not adequate to draw any conclusions due to very small sample size. The sponsor has provided a justification that the follow-up information not available on 9 patients. These patients did not return for follow-up evaluation (NDA read was negative for these patients).

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 200-655 Resubmission Document Number 19, Re-submission after Refuse to File
Drug Name:	Flurodopa F 18 (FDOPA) injection - PET Imaging drug
Indication(s):	Fluorodopa F 18 Injection is a [redacted (b) (4)] used in Positron Emission Tomography (PET) to visualize dopaminergic [redacted (b) (4)] in the striatum [redacted (b) (4)] adult patients with suspected parkinsonian syndromes (PS). [redacted (b) (4)] . Fluorodopa F 18 PET is an adjunct to other diagnostic investigations
Applicant:	Feinstein Institute medical Research via Thomas Chaly, Ph.D.
Date(s):	NDA Submission: December 15, 2015 PDUFA Date: June 15, 2015
Review Priority:	Resubmission – Class 2
Biometrics Division:	OB/DBV
Statistical Reviewer:	Satish Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Secondary Reviewer Thomas E. Gwise, Ph. D., Deputy Director Division of Biostatistics V
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Brenda Ye, M. D. Clinical TL/DD: Alex Gorovets, M. D. / Louis Marzella, M. D.
Project Manager:	Thuy Nguyen

Keywords: Expanded Access IND, complete response, mean, standard deviation, Sensitivity, Specificity

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1. EXECUTIVE SUMMARY

The standard of truth (SOT) for the sponsor's original submission was each patient's clinical diagnosis at the time of referral for a Fluorodopa F 18 PET scan as the standard of truth for measuring the test's performance characteristics. This standard was not considered adequate and clinically meaningful in the CR letter. The supplicant was advised by DMIP to conduct a new study to address clinical deficiencies cited in the CR letter.

The sponsor conducted and provided the result of a new prospective clinical study (Study # 17). The standard of truth (SOT) for this study was follow-up by the referring physician up to 1 year and in some cases up to 2 years to determine SOT. This was based on advice in the CR letter – "obtain the standard of reference (follow-up clinical diagnosis) in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18 PET negative patients." There are sources of bias in determining the SOT. The final diagnosis was made by the same referring physician who also had knowledge of F-DOPA scan results. The entrance to the study was limited to patients who were willing to pay for this diagnostic method. The SOT could not be determined due to lack of follow-up response for scan negative patients (7/13 or 54%).

The study (#17) enrolled 45 subjects referred by neurologists based on the parkinsonian syndrome. Images were evaluated by three separate onsite readers. Each reader evaluated the scans and reported the result as either positive or negative. Visual assessment of the striatal region in a Fluorodopa F 18 PET scan provided either a positive (Striatal Dopaminergic Neuronal Loss [SDNL] present) or negative (no SDNL present) result. The visual assessment was validated by follow up studies (SOT) with the referring physicians. All 3 readers agreed on 44 out of 45 scans (98%). Two (2) out of 3 readers agreed on all 45 out of 45 scans (100%). In the study # 15/16 submitted in the original submission, there was no variability among three scan readers with regards to the visual assessment of the PET scans. The three blinded PET scan readers were also blinded to the physicians' diagnosis.

The total number of patients referred to The Feinstein Institute for Medical Research for this study was 45. Out of 45 patients, 32 had positive PET scans and 13 had negative PET scans. Out of 32 positive PET 30 patients were followed up and had positive PET scan results. Two patients who had positive PET scan results have a pending SOT. Out of the 13 negative scans, 6 patients were followed up and had SOTs determined (negative) and the other 7 are pending. The sensitivity for 30 patients that were followed-up was 100% (95% CI (88, 100%) and specificity for 6 out of 13 patients who had follow-up SOT was also 100% with 95% CI (54-100%). In the previously submitted study # 15/16 with the primary endpoint of the visualization of the striatal region using Fluorodopa F 18 PET, there were no false positive or false negative scan results considering physician's clinical diagnosis as SOT, resulting in 100% sensitivity and 100% specificity.

This study also has limitations related to establishing SOT and substantial number of patients in the negative PET scans group (7 out of 13 – 54%) did not have SOT determined due to non-response during follow-up telephone calls.

This study # 17 provides additional clinical evidence. Based on the results from the collective clinical evidence (results of study # 15/16 and 21 together with study # 17) and the sponsor

following DMIP guidance, there is some clinical utility for F-DPOA PET imaging in a selected patient population.

The division has planned an SGE review the FDOPA PET images from the 45 patients in the clinical trial # 17 to confirm that they are consistent with the clinical presentation of condition by the sponsor.

2. INTRODUCTION

Fluorodopa, also known as F-DOPA, is a fluorinated form of Levodopa (L-DOPA) primarily synthesized as its fluorine-18 isotopologue for use as a radiotracer in positron emission tomography (PET). Positron emission tomography (PET) is a nuclear medical imaging technique that produces a three-dimensional image or picture of functional processes in the body. PET technology using short-lived radioisotopes is a state of the art imaging technology.

Fluorodopa F 18 Injection belongs to the aromatic amino acid class of compounds. Once injected, Fluorodopa F 18 will cross the blood brain barrier to reach the striatal region where it undergoes decarboxylation to form fluorodopamine. As in the case of L-DOPA, the storage of the fluorodopamine in the striatum will depend upon the condition of the striatal region. Therefore, the storage of fluorodopamine F 18 in the striatum will depend upon the extent of neuronal loss. If the striatal region has no loss of dopaminergic neurons, Fluorodopa F 18 uptake in that region will be normal. However, if there is dopaminergic neuronal loss in the striatum, the uptake of fluorodopamine will be reduced depending upon the extent of the neuronal loss. According to the sponsor, (b) (4) Fluorodopa F 18 follows the same biological pathway as L-DOPA and the drug is excreted through the bladder in a similar way. The sponsor states that the safety and effectiveness of L-DOPA is well established.

This radiotracer (F-DOPA) has already been approved by the European Union a long time back as a diagnostic imaging for the differential diagnosis of parkinsonian syndromes. Fluorodopa F 18 PET has been used for the last 20 years around the world. The sponsor points out that Fluorodopa F 18 PET was approved in France in 2010 followed by several countries in the European Union. In Europe several pharmaceutical companies have received marketing authority for Fluorodopa F 18 Injection.

2.1 Overview

The safety and efficacy of Fluorodopa F 18 Injection was presented by the FDA reviewers at the public meeting conducted by FDA on July 28, 2000. It was pointed out that the available literature data were insufficient to support efficacy in any patient population. A pre-IND meeting was held in 2008 and original NDA was submitted on 10/29/2009 with a PDUFA start date of 1/ 21/2010 (date user fee waiver granted). Refuse to File letter was issued on 3/19/2010.

The sponsor re-submitted a 505(b)(2) NDA after refuse to file. In this NDA (# 200655), the applicant submitted information on 9 studies. All these studies were post-hoc evaluation including primary clinical study # 15 conducted by the sponsor. Eight (8) out of 9 studies were from literature publications. Three (3) out of 9 studies were found relevant for evaluating diagnostic efficacy (performance characteristics) of Fluorodopa F 18 (F-DOPA) injection, but all had deficiencies. Two studies (# 15 & # 16) were retrospective, single center, and with clinical diagnosis (after Parkinson's drug treatment response or non-response) of "Possible PD", "Possible non-PD" and "Suspected non-PD " as Standard of Truth (SOT). Using this standard of truth, the applicant concluded the performance characteristics of 100% sensitivity, and 100% specificity for the study. A protocol for study # 15 was not submitted to the Agency for review.

Study #16 was a continuation of the clinical study # 15 by the applicant to further evaluate the patients that exhibited Parkinsonian symptoms but had a negative fluorodopa F 18 scan. The applicant states that the 27 patients with negative scans were followed for 2-4 years. A further amendment (April 5, 2013) by the applicant listed only eight patients out of 27 F-18 FDOPA PET negative patients from Study #15 were followed to obtain patient's final clinical diagnosis. Clinical data from such a small number of patients and with so much missing data do not provide a reliable assessment of the performance characteristics of fluorodopa F 18.

Study # 21 was exploratory, single center with all study patients already diagnosed with PD (not the target patient population), and it is unclear how specificity and sensitivity were calculated.

The clinical value in terms of providing differential diagnosis of patients with parkinsonian symptoms or proving supplemental value to physician's clinical diagnosis was not established in these retrospective studies.

A complete response letter was issued by FDA on 10-22-2013. Deficiencies cited included lack of adequate and well controlled clinical trials; significant deficiencies in the referenced literature studies and in the studies conducted by the sponsor in support of this application. The data submitted in this application were not sufficient for evaluating the (b) (4) usefulness of Fluorodopa F 18 PET in the proposed patient population. The details of the CR letter related to clinical/statistical issues are given in Appendix A.

Feinstein Institute was approved by FDA annually to continue using Fluorodopa F 18 Injection under an Expanded Access IND 78861.

The sponsor submitted response to FDA for the "Complete Response letter dated 10/22/2013 for the NDA 200655" on 12-15-2015. The sponsor conducted a prospective clinical study based on the IRB/FDA approved protocol to evaluate the sensitivity, specificity, and usefulness of Fluorodopa F 18 Injection PET studies for patients with suspected cases of Parkinsonian syndromes under the FDA approved Expanded Access IND. The sponsor pointed out that the Fluorodopa Expanded Access IND was not reimbursed by CMS and therefore depended upon patients who were willing to pay for the clinical studies. There was no obligation for the patients to return to the referring physician for the follow up SOT after a particular period of time. This resulted in assessing SOT for some patients. All patients in the study had signed consent forms and the consent for the follow up for the SOT.

The focus of this review is response from the sponsor related to CR letter issued by FDA.

2.1.1 Indication and Doses

Proposed indication: Fluorodopa F 18 Injection is a [redacted] used in Positron Emission Tomography (PET) to visualize dopaminergic [redacted] in the striatum [redacted] adult patients with suspected parkinsonian syndromes (PS). [redacted]. Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.

The proposed dosage form is injection: Recommended dose for adults is [redacted] 5.0 mCi ([redacted] 0.185 GBq), Route of Administration is intravenous. At the Feinstein Institute, subjects were dosed with 150 mg of carbidopa approximately 60-90 minutes prior to administration of Fluorodopa F 18 Injection dose between 4.05 -5.0 mCi to generate a well resolved image. Fluorodopa F18 is not recommended for pediatric patients. Fluorodopa F 18 is an imaging agent and is not for treatment purposes.

2.1.2 Identified Study in the review

In the complete response, FDA suggested to conduct a new prospective study that could potentially address issues in the CR letter. The sponsor completed a clinical study (study # 17) based on the IRB/FDA approved protocol. The title of the study is:

STUDY# 17: Clinical Study of Fluorodopa F 18 Injection Conducted by the Feinstein Institute for Medical Research, 350 Community Drive, Manhasset, New York 11030

2.2 Data Sources

Electronic datasets were submitted as a result of Information Request sent to the sponsor on 18 Feb. 2016. The data were submitted in SAS xpt format on 25 Feb. 2016.

The NDA in eCTD located at: \\CDSESUB4\NONECTD\NDA200655\5967723

3. STATISTICAL EVALUATION

The sponsor conducted a new prospective clinical study (study # 17, n=45) based on the IRB/FDA approved protocol to evaluate the sensitivity, specificity, and usefulness of Fluorodopa F 18 Injection PET studies with suspected cases of Parkinsonian syndromes. The sponsor states that Fluorodopa F 18 PET (b) (4) At the onset of PD and related diseases, the patients will have a loss of dopaminergic neurons in the range of 45 to 50%. This loss will be reflected in the PET scan based on the reduced uptake of Fluorodopa F 18 in the striatum. Patients with Parkinson's or related disease (Parkinsonism) will indicate a loss of dopaminergic neurons in the striatum depending upon the severity of the disease (a reduced uptake of Fluorodopa F 18 in the putamen or putamen and caudate unilaterally or bilaterally with the loss of dopaminergic neurons). Patients with essential tremor will have no dopaminergic neuronal loss and the PET scans will be normal. (b) (4) . Patients with confirmed Parkinson's disease are treated differently from patients with essential tremor. Therefore, a differential diagnosis for patients with parkinsonian syndromes is essential for the proper management of these two diseases.

3.1 Data and Analysis Quality

There was one prospective study (#17) in response to CR letter conducted by the applicant (Feinstein Inst.). The applicant submitted patient level data in proper SAS xpt format.

3.2 Evaluation of Efficacy

3.2.1 Objective

- To determine the sensitivity, specificity, and usefulness of Fluorodopa PET for the differential diagnosis of parkinsonian syndromes.
- To determine the inter-rater-reliability of the readers of the PET scan.
- To determine how quantitative measures for PET correlate with PD diagnosis.
- To monitor safety by visual observation of patients.

3.2.2 Primary Criteria for evaluation

The primary efficacy measure was visualization of the size and shape of the putamen/ caudate in the striatum. The visual assessment of PET scan images was done by three qualified readers as either positive (loss of dopaminergic neurons - demonstrated a reduced uptake of Fluorodopa F 18 Injection) or negative (no loss of dopaminergic neurons - showed a normal uptake of Flurodopa F 18). The patients were followed up one to two years past the date of their PET

scan in order to establish the standard of truth (SOT). In some cases the SOT was received earlier than a year based on the decision by the referring physician. The protocol defined plan was to collect SOT's from 20-30 patients to establish sensitivity and specificity for this study.

3.2.3 Inclusion Criteria

All patients in this study were referred by Neurologists and exhibited at least one of the cardinal features of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). The referring physicians were not sure whether the patients have Parkinsonism (Loss of dopaminergic neurons in the striatum) or essential tremor (no loss of dopaminergic neurons). The patients were referred directly to the patient scheduling center of The Feinstein Institute for Medical Research. No specific populations have been studied in this clinical study.

3.2.4 Number of Subjects

The total number of patients referred to The Feinstein Institute for Medical Research for this study was 45. Out of 45 patients, 32 had positive PET scans and 13 had negative PET scans. Out of 32 positive PET 30 patients were followed up and had positive PET scan results. Two patients who had positive PET scan results have a pending SOT. Out of the 13 negative scans, 6 patients were followed up and had and had SOTs determined (negative) and the other 7 are pending. Several attempts were made to collect SOT's from the referring physicians for the 7 patients, but were not successful. The sponsor stated that it was difficult to collect SOT's from patients with negative PET scans. Protocol defined plan was to collect SOT's from 20-30 patients to establish sensitivity and specificity for this study.

3.2.5 Demographic and Baseline Characteristics

The study population for efficacy in Study 17 includes 45 adults. The characteristics of subjects are given in the following Table 2.

Table 1: Characteristics of Subjects According to Gender
(mean ± SD)

Characteristic	Male (n=32, 71%)	Female (n = 13, 29%)	All (n =45)
Age (Mean ± SD)	60.3 ± 12.4	54.2 ± 14.1	55.6 ± 13.1
Patients with Loss of Dopaminergic Neurons	24 (75%)	8 (25%)	32
Patients with No Loss of Dopaminergic Neurons	8 (61.5%)	5 (38.5%)	13

3.2.6 Primary Endpoint

The primary endpoint for this study was the visualization of either the loss or no loss of dopaminergic neurons in the striatum. Visualization was based on the assessment of the shape and size of the putamen/caudate region. The clinical endpoint is the differentiation of patients with Parkinsonism (IPD, CBD, PSP, etc.) from essential tremor and related diseases (DRD, SWEDD, etc.) based on the PET scan results. Patients with essential tremor are expected to have normal (negative) PET scans indicating that their clinical symptoms were not in fact due to IPD or related diseases. Fluorodopa F18 PET is not indicated to differentiate between PD, MSA, or PSP.

3.2.7 Readers and Image Evaluation

The PET scans were evaluated visually by 3 readers. Visual interpretation of the scans were recorded either as positive (loss of dopaminergic neurons) or negative (no loss of dopaminergic neurons). The reliability of the visual detection was assessed based on the interpretation of the PET scan by the 3 readers. A reduced uptake of Fluorodopa F 18 Injection in the putamen or both putamen and caudate, unilaterally or bilaterally indicates the loss of dopaminergic neurons. Any loss of dopaminergic neurons in the striatum will appear as a reduction in the size of the crescent-shaped region in the PET scan.

3.3 Results and Conclusions

There were 45 patients enrolled in this study. Patients were referred by neurologists based on the parkinsonian syndrome. Images were evaluated by three separate onsite readers. Each reader evaluated the scans and reported the result as either positive or negative. A positive scan shows a reduced uptake of Fluorodopa F 18 by the putamen or putamen/caudate, either unilaterally or bilaterally, depending upon the severity of the disease. Negative scans were characterized based on the uptake of Fluorodopa F 18 by the caudate and putamen bilaterally. Negative scans show a uniform uptake, as seen by the crescent shaped caudate and putamen.

Visual assessment of the striatal region in a Fluorodopa F 18 PET scan provided either a positive (Striatal Dopaminergic Neuronal Loss [SDNL] present) or negative (no SDNL present) result. The visual assessment was validated by follow up studies (SOT) with the referring physicians.

Out of the 45 subjects, 7 subjects with negative scans did not go back to their referring physician to record the SOT. Attempts were made 3 times in each case to get the SOT from these patients but there was no response. Supporting documents were included in their chart. Two patients who had positive PET scan results have a pending SOT In the case of PD patients the response was fast.

Under Parkinsonism, the main group is Idiopathic Parkinson's Disease (IPD) or generally called PD. The second group is Atypical Parkinson's (APD). Based on the experience in the medical management of these patients, some of these patients under APD are grouped as Cortical Basal

Ganglion Degeneration (CBD), Progressive Supra-Nuclear Palsy (PSP), Multiple System Atrophy (MSA), Gait Freezing, etc. by the physicians. In rare cases where patients have a normal PET scan, the physicians have listed MSA along with essential tremor. In the case of patients with parkinsonian syndromes and a normal PET scan, the physicians have grouped them as Essential Tremor (ET), Dopamine Responsive Dystonia (DRD), Subject without Evidence of Dopaminergic Deficit (SWEDD,) etc. Therefore, the referring physicians have used these classifications when reporting the SOT.

The details are provided in Table 3. The results of visual assessment of the striatal region in a Fluorodopa F 18 PET scan by 3 readers are:

- All 3 readers agreed on 44 out of 45 scans (98%)
- Two (2) out of 3 readers agreed on all 45 out of 45 scans (100%).

Table 2: Clinical Diagnosis at Referral, Reader's Evaluation, Final Diagnosis & Follow-up SOT

Sub. ID #	Clinical Diagnosis at referral	Readers #			Scan Reading	Follow-up SOT
		1	2	3		
(b) (4)						

ET – Essential Tremor
DRD = Dopamine Responsive Dystonia
MSA = Multiple System Atrophy
SWEDD = Subject Without Evidence of Dopaminergic Deficit
CBD = Cortical Basal Ganglion Degeneration

Sensitivity and specificity:

Sensitivity and specificity were computed for those with a known SOT. There were four categories of sensitivity and specificity - calculations depending on whether MSA was considered a dopamine loss condition and or whether freezing gait was considered a dopamine loss condition. Category 1 corresponds to sensitivity and specificity when freezing gait is considered a dopamine loss and MSA is not considered a dopamine loss. Category 2 is the computation of sensitivity and specificity when freezing gait is considered a dopamine loss and MSA is also considered a dopamine loss. Category 3 is the calculation of sensitivity and specificity when freezing gait is not considered a dopamine loss and MSA is also not considered a dopamine loss. Finally, Category 4 is the calculation of sensitivity and specificity when freezing gait is not considered a dopamine loss and MSA is considered a dopamine loss. The results are provided in the following Table 4:

Table 3: Sensitivity and Specificity

	Category 1	Category 2	Category 3	Category 4
Freezing Gait	DOPA Loss	DOPA Loss	No DOPA Loss	No DOPA Loss
MSA	No DOPA Loss	DOPA Loss	No DOPA Loss	DOPA Loss
Sensitivity 95% CI	30/30 = 100% (88, 100%)	30/31 = 96.8% (83, 99.9%)	29/29= 100% (88, 100%)	29/30 = 96.7% (83, 99.9%)
Specificity 95% CI	6/6= 100°/o (54, 100%)	5/5 =100% (48, 100%)	6/7=85.7% (42, 99.6%)	6/7 =85.7% (42, 99.6%)
PPV* 95% CI	30/30 = 100% (88, 100%)	30/30 = 100% (88, 100%)	29/30 = 96.7% (83, 99.9%)	29/30 = 96.7% (83, 99.9%)
NPV** 95% CI	6/6 = 100% (54, 100%)	5/6 = 83.3% (36, 99.6%)	6/6 = 100% (54, 100%)	5/6 = 83.3% (36, 99.6%)

*Positive Predictive Value
**Negative Predictive Value

The point estimates of the sensitivity ranged from 97% to 100% with 95% CI ranging from 83 – 100%. The point estimates of the specificity ranged from 96% to 100% with 95% CI ranging from 42 – 100%. In the previously submitted study # 15 with the primary endpoint of the visualization of the striatal region using Fluorodopa F 18 PET, there were no false positive or false negative scan results considering physician's clinical diagnosis as SOT, resulting in 100% sensitivity and 100% specificity.

3.4 Evaluation of Safety

Applicant states that F 18 is a short-lived radioisotope, at the end of the study there is only trace amounts of radiation left in the brain and the patient has minimal radiation risk. There were no adverse events after the administration of Fluorodopa F 18 and there was no premature discontinuation from the study due to complication. There have been no safety concerns from over 20 years of use of the drug at the Feinstein Institute. This is a derivative of L-dopa, which has a known safety profile.

Patients in this study # 17were monitored visually for any physical discomfort. Patient charts did not indicate any safety issue. After the PET scans, all patients were followed up with a phone call within 24 hours to collect information regarding any possible adverse events. All patients responded to phone call, except one patient. Among the responding patients (44/45) there were five cases in which the patients had minor events. The Principal Investigator (PI) contacted the patients to investigate the nature of the adverse events. In all cases, after discussing with the patients, the PI concluded that the minor adverse events were not caused by the administration of Fluorodopa F 18 Injection.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

For the study # 17, findings were assessed for each of the primary variables by gender and age. The results indicated a general consistency across each stratification for each reader. There was no difference in the efficacy data obtained from the male and female group of patients either in this study.

Since Fluorodopa F 18 is used in different regions around the world, the subject population includes people with a wide range of ethnic backgrounds. Males and females of various ages, heights and weights were also included. According to the applicant, there is no indication that the drug behaves differently in any specific subpopulation. There were no observable differences in the PET images among subjects due to any type of characteristic other than disease state. As no adverse events have been reported, there is also no indication that Fluorodopa F 18 Injection would pose a risk to any subpopulation.

4.2 Other Special/Subgroup Populations

Patients with a long term clinical history (over 5 years) were identified as a special subgroup of interest for the study # 17. Out of the 45 patients, there were 11 patients (10 male; 1 female) exceeding 5 years of disease duration. In 11 patients, 7 had a positive PET scan and 4 patients had a negative scan. The SOT was received for all 7 patients who had a positive scan and the SOT confirmed PD (sensitivity = 100%). Four patients with a negative scan have pending SOT's (specificity could not be computed).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor provided the result of a new prospective clinical study (Study # 17). This study was conducted based on the IRB/FDA approved protocol to evaluate the sensitivity, specificity, and usefulness of Fluorodopa F 18 Injection PET studies for patients with suspected cases of Parkinsonian syndromes. The protocol was also to satisfy the physicians request to study parkinsonian patients under the FDA approved Expanded Access IND. Since the Fluorodopa Expanded Access IND was not reimbursed by CMS, the sponsor pointed out that they had to depend upon patients who were willing to pay for the clinical studies. There was no obligation for the patients to return to the referring physician for the follow up SOT after a particular period of time. There were limitations and sources of bias in this study.

This was a single center study and enrollment in the study was limited to patients who were willing to pay for the clinical studies and referred by their neurologist. Follow-up clinical diagnosis in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18 PET negative patients was expected. The total number of patients referred to The Feinstein Institute for Medical Research for this study was 45. Out of 45 patients, 32 had positive PET scans and 13 had negative PET scans. Out of 32 positive PET 30 patients were followed up and had positive PET scan results. Two patients who had positive PET scan results have a pending SOT. Out of the 13 negative scans, 6 patients were followed up and had and had SOTs determined (negative) and the other 7 are pending. The truth for negative patients was determined only for 6 patients out of 13 negative patients.

5.2 Conclusions and Recommendations

The standard of truth (SOT) for the sponsor's original submission was each patient's clinical diagnosis at the time of referral for a Fluorodopa F 18 PET scan as the standard of truth for measuring the test's performance characteristics. This standard was not considered adequate and clinically meaningful in the CR letter. The supplicant was advised by DMIP to conduct a new study to address clinical deficiencies cited in the CR letter.

The sponsor conducted and provided the result of a new prospective clinical study (Study # 17). The standard of truth (SOT) for this study was follow-up by the referring physician up to 1 year and in some cases up to 2 years to determine SOT. This was based on advice in the CR letter – "obtain the standard of reference (follow-up clinical diagnosis) in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18 PET negative patients." There are sources of bias in determining the SOT. The final diagnosis was made by the same referring physician who also had knowledge of F-DOPA scan results. The entrance to the study was limited to patients who were willing to pay for this diagnostic method. The SOT could not be determined due to lack of follow-up response for scan negative patients (7/13 or 54%).

The study (#17) enrolled 45 subjects referred by neurologists based on the parkinsonian syndrome. Images were evaluated by three separate onsite readers. Each reader evaluated the scans and reported the result as either positive or negative. Visual assessment of the striatal

region in a Fluorodopa F 18 PET scan provided either a positive (Striatal Dopaminergic Neuronal Loss [SDNL] present) or negative (no SDNL present) result. The visual assessment was validated by follow up studies (SOT) with the referring physicians. All 3 readers agreed on 44 out of 45 scans (98%). Two (2) out of 3 readers agreed on all 45 out of 45 scans (100%). In the study # 15/16 submitted in the original submission, there was no variability among three scan readers with regards to the visual assessment of the PET scans. The three blinded PET scan readers were also blinded to the physicians' diagnosis.

The total number of patients referred to The Feinstein Institute for Medical Research for this study was 45. Out of 45 patients, 32 had positive PET scans and 13 had negative PET scans. Out of 32 positive PET 30 patients were followed up and had positive PET scan results. Two patients who had positive PET scan results have a pending SOT. Out of the 13 negative scans, 6 patients were followed up and had SOTs determined (negative) and the other 7 are pending. The sensitivity for 30 patients that were followed-up was 100% (95% CI (88, 100%) and specificity for 6 out of 13 patients who had follow-up SOT was also 100% with 95% CI (54-100%). In the previously submitted study # 15/16 with the primary endpoint of the visualization of the striatal region using Fluorodopa F 18 PET, there were no false positive or false negative scan results considering physician's clinical diagnosis as SOT, resulting in 100% sensitivity and 100% specificity.

This study also has limitations related to establishing SOT and substantial number of patients in the negative PET scans group (7 out of 13 – 54%) did not have SOT determined due to non-response during follow-up telephone calls.

This study # 17 provides additional clinical evidence. Based on the results from the collective clinical evidence (results of study # 15/16 and 21 together with study # 17) and the sponsor following DMIP guidance, there is some clinical utility for F-DPOA PET imaging in a selected patient population.

The division has planned an SGE review the FDOPA PET images from the 45 patients in the clinical trial # 17 to confirm that they are consistent with the clinical presentation of condition by the sponsor.

SIGNATURES/DISTRIBUTION LIST

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Date: April 15, 2016

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File: C:\CDER\2016 IND NDA\NDA 200-655 F-DOPA Stat Review 15April2016.doc

Appendix A: Clinical/Statistical issues identified in CR letter and Recommendations

Your application contains no data from adequate and well controlled clinical trials. Significant deficiencies have been identified in the referenced literature studies and in the studies you have conducted in support of this application. The data submitted in your application are not sufficient for evaluating the diagnostic effectiveness and usefulness of Fluorodopa F 18 PET in the proposed patient population.

1. The following deficiencies have been identified with clinical Study #15, which was conducted at the Feinstein Institute of Medical Research:

    a. The study is a retrospective, single center study.

    b. The study was not conducted according to a pre-specified protocol, and hence, definitions of the primary efficacy endpoint and the standard of truth that would normally be specified by a protocol, are not well-defined for the study.

    c. The study used each patient's clinical diagnosis at the time of referral for a Fluorodopa F 18 PET scan as the standard of truth for measuring the test's performance characteristics. We do not find such a standard to be clinically meaningful and do not agree with the cited diagnostic performance measurements of Fluorodopa F 18 as 100% for sensitivity and 100% for specificity.

    d. Of the 185 study patients, 158 patients had a pre-imaging clinical diagnosis of Parkinson's disease and were responding to Parkinson's disease medications. For these patients a Fluorodopa F 18 PET scan provides no additional clinically useful information. Deficiencies concerning the remaining 27 study patients are discussed below (Study #16).

    e. You have provided no documentation that Fluorodopa F 18 PET images have been read independently by three readers blinded to clinical information. Furthermore, inspection of the study site revealed that none of the 47 audited cases contained documentation that each patient's images were read by three blinded readers.

2. Study #16 is a publication with the follow-up results of 27 Fluorodopa F 18 PET negative patients enrolled in Study #15. Study #16 has the following major deficiencies:

    a. Per your amendment dated April 5, 2013, only 8 of the 27 Fluorodopa F 18 PET negative patients from Study #15 were

followed for 2 to 4 years to obtain the patient's final clinical diagnosis. Clinical data from such a small number of patients do not provide a reliable assessment of the performance characteristics of Fluorodopa F 18 PET. Furthermore, inspection of the study site revealed that none of the subject files contained documentation (clinical follow-up confirmation) of the continued absence of classical Parkinson's Disease symptoms and signs.

b. The reasons for not obtaining follow up on the remaining 19 patients are not provided.

3. Among the remaining literature publications in your application (Studies #17-23), only the publication by Eshuis et al. (Study #21) provides clinical data for the assessment of the efficacy of Fluorodopa F 18 as a diagnostic radiopharmaceutical. However, Study #21 does not provide substantial evidence of efficacy for the following reasons:

a. The study is a small single center study and is exploratory in design.

b. All study patients had a diagnosis of Parkinson's disease at the time of enrollment. The study excluded patients with atypical signs and patients not responding to Parkinson's disease medication. Therefore, the study does not evaluate a patient population that might benefit from a diagnostic imaging test.

c. The definition of positive scans (mean standard uptake value in patients below two standard deviations of the mean in healthy controls) is an exploratory quantitative measure and its threshold is arbitrarily set.

To address these deficiencies, we recommend the following:

1. Conduct an adequate and well-controlled clinical trial which might provide substantial evidence of effectiveness of Fluorodopa F 18 in the intended patient population. We encourage you to develop such a study using a pre-defined standard of reference for measuring the performance characteristics (sensitivity and specificity) of Fluorodopa F 18, a pre-specified statistical analysis plan, and image interpretations made by independent readers blinded to clinical information. Note in order to measure the sensitivity and specificity of Fluorodopa F 18, you need to obtain the standard of reference (follow-up clinical diagnosis) in both Fluorodopa F 18 PET positive patients and Fluorodopa F 18 PET negative patients. You should use as a standard of reference the clinical diagnosis made by a movement disorder specialist at a predefined time interval following the Fluorodopa F 18 PET scan.

2. The study population must include subjects who might benefit from the Fluorodopa F 18 PET scan. Such patients could include those in whom Parkinsonian and essential tremor could not be differentiated on clinical grounds, those with suspected early onset of Parkinsonian syndrome, and/or those not responding to a Parkinson disease medication.

   To facilitate the interpretation of the study's results, we recommend that you consider exclusion of subjects with features suggestive of multiple system atrophy or progressive supranuclear palsy, response to Parkinson's disease medication, a clinical history exceeding five years, and concomitant medication known or suspected of interacting with striatal uptake of Fluorodopa F 18.

3. We reference the Good Clinical Practice (GCP) deficiencies identified during our inspection of your clinical study site and communicated to you on March 22, 2013. These deficiencies call into question the reliability of the clinical data in your application. It is necessary to conduct a study in compliance with GCP standards to ensure the quality and integrity of the data.

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/s/

SATISH C MISRA
04/26/2016

JYOTI ZALKIKAR
04/26/2016

Proposed indication for this drug is for Positron Emission Tomography (PET) to visualize dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes. Sensitivity and specificity are not appropriate measures for the proposed indication. Primary reviewer has mentioned few limitations of the clinical study (#17) in this re-submission, but that list is not comprehensive. Please see secondary review for other issues and recommendations.

THOMAS E GWISE
04/27/2016

The method used to determine the true state of each patient with respect to the condition of interest may confound the results of the study. Please see secondary review for further comments.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 200-655 Resubmission Document Number 19
Drug Name:	Flurodopa F 18 (FDOPA) injection - PET Imaging drug
Indication(s):	Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET) to visualize the loss of dopaminergic (b) (4) in the striatum (b) (4) adult patients with suspected parkinsonian syndromes (PS). Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.
Applicant:	Feinstein Institute medical Research
Date(s):	NDA Submission: December 15, 2015 PDUFA Date: June 15, 2015
Review Priority:	Resubmission – Class 2
Biometrics Division:	OB/DBV
Secondary Reviewer:	Jyoti Zalkikar, Ph. D.
Concurring Reviewers:	Thomas E. Gwise, Ph. D., Deputy Director Division of Biostatistics V
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Brenda Ye, M. D. Clinical TL/DD: Alex Gorovets, M. D. / Louis Marzella, M. D.
Project Manager:	Thuy Nguyen

Keywords: Positive percent agreement, Negative percent agreement, non-response

Executive Summary

This resubmission of NDA 200655 for Fluorodopa F 18 (FDOPA) consists of a response to FDA's Complete Response letter given to the applicant in 2013, in terms of submission of results from a new clinical trial (#17) that the applicant conducted. Details of previous communications between the applicant and FDA as well as the information about this drug can be found in the primary statistical review.

The safety and efficacy of FDOPA (short-lived radiopharmaceutical used in Positron Emission Tomography (PET)) were evaluated in one single-center, single-arm study (Study #17) that evaluated 45 adult patients with suspected parkinsonian syndromes (PS)). In this study, FDOPA image outcomes were compared to a reference clinical diagnostic standard of "PS" or "non-PS". The reference clinical diagnostic standard for "PS" consisted of the following diagnoses: Parkinson's disease (PD), multiple system atrophy (MSA), Gait Freeze, Cortical Basal Ganglion Degeneration (CBD), Pisa Syndrome, and progressive supra-nuclear palsy (PSP). The applicant considered that these conditions have been associated with the loss of dopaminergic neurons. FDOPA imaging was not designed to distinguish among the conditions. The reference clinical diagnostic standard for "non-PS", according to the applicant, consisted of an essential tremor (ET) diagnosis, or other non-PS diagnosis (Dopamine Responsive Dystonia (DRD), Subject without Evidence of Dopaminergic Deficit (SWEDD)). Sixty-five to 100 minutes after FDOPA administration by intravenous injection (150-185 MBq, 4.05-5.0 mCi), subjects underwent PET scan and attenuation correction.

The primary end point for this study was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." "Loss" of dopaminergic neurons in the striatum was based upon the reader's judgment of what a "no loss" image looks like, not upon a prior scan in the same patient.

Limitations of this study are as follows: FDOPA images were evaluated by 3 on-site readers. It is not clear from the applicant's report whether these readers were blinded to clinical information or not; and whether these readers were independent or not. It is also not clear whether these readers had any other role in patient assessment or not. The reference clinical diagnostic standard is the clinical diagnoses established by a referring physician after at least 1 year of follow-up. This reference clinical diagnostic standard is available in 36 out of 45 patients in this study. The applicant calls this reference standard as standard of truth (SOT) which is not appropriate, neither are the applicant's calculations of sensitivity and specificity. These are not appropriate performance characteristics for this study, where the primary endpoint is visualization of dopaminergic neurons. Sensitivity and specificity are appropriate when the TRUTH standard (independent from imaging, for example autopsy results) is available. Here, in the study, we have reference standard for visualization, not truth standard for PS disease.

Among the 45 patients in Study # 17, 29% (13/45) were female and the average age was 58.6 years (standard deviation = 13.1); the baseline clinical diagnoses consisted of: probable PD, possible PD, possible ET, and other diagnoses. Table below shows the appropriate visualization parameters, positive percent agreement and negative percent agreement of the FDOPA image results with the reference clinical diagnostic standard, defined as follows.

Positive percent agreement represents the percent of patients with abnormal (positive) FDOPA images among all the patients with a clinical diagnostic reference standard of PS. The sample size for this agreement measure in this study is 31.

The negative percent agreement represents the percent of patients with normal (negative) FDOPA images among the patients with a non-PS clinical diagnostic reference standard. The sample size for this agreement measure in this study is 5, which is too small to draw any conclusions.

The applicant should have raised their sample-size to at least 200 patients, given the 20% non-response to reference clinical diagnostic standard and 14% "non-PS" patients.

Positive and Negative Percent Agreements for Study# 17

	Positive percent agreement (% patients with an abnormal FDOPA image among patients with PS, N=31)	Negative percent agreement (% patients with a normal FDOPA image among patients with non-PS, N=5)
Reader 1	29/31=94%	5/5=100%
Reader 2	30/31=97%	5/5=100%
Reader 3	30/31=97%	5/5=100%

The FDA is currently planning to have an SGE review the FDOPA images from this study to confirm that the applicant's results are consistent with the clinical presentation of condition.

The effectiveness of FDOPA as a confirmatory test for monitoring disease progression or response to therapy has not been established.

The applicant collected Striatal-Occipital Ratio (SOR) in Study 17. Striatal Occipital Ratio is the ratio of radioactivity in the striatum (target) to that of the occipital cortex (background). These SOR values were not used for the visual interpretation of the PET scan results in this study. The clinical pharmacology reviewer's analysis of the data showed that, on average, SOR differed as a function of disease. However, because there was considerable overlap between SORs in patients with Parkinson's and healthy subjects, SOR cannot be used as an aid to scan interpretation.

This secondary reviewer recommends that the applicant be given, again, a complete response letter citing the limitations (clinical/statistical and compliance with good clinical practice (GCP)) of their clinical study #17.

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/s/

JYOTI ZALKIKAR
04/22/2016

THOMAS E GWISE
04/22/2016

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 200-655 Document Number 19, Re-submission after Refuse to File
Drug Name:	Flurodopa F 18 (FDOPA) injection - PET Imaging drug
Indication(s):	Fluorodopa F 18 PET is indicated to [redacted] (b) (4) in the striatum of adult patients with suspected Parkinsonian syndromes (PS).
Applicant:	Feinstein Institute via Thomas Chaly, Ph.D.
Date(s):	NDA Submission: October 22, 2012 PDUFA Date: October 22, 2013
Review Priority:	Standard
Biometrics Division:	OB/DBV
Statistical Reviewer:	Satish Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D., Team Leader Thomas E. Gwise, Ph. D., Deputy Director Division of Biostatistics V
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Clinical: Brenda Ye, M. D. Clinical TL/DD: Alex Gorovets, M. D. / Louis Marzella, M. D.
Project Manager:	Thuy Nguyen

Keywords: Expanded Access IND, complete response, mean, standard deviation, Sensitivity, Specificity

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1. EXECUTIVE SUMMARY

In this NDA (# 200655), the applicant submitted information on 9 studies. All these studies are post-hoc evaluation including primary clinical study # 15 conducted by the sponsor. Eight (8) out of 9 studies are from literature publications. Three (3) out of 9 studies were found relevant for evaluating diagnostic efficacy (performance characteristics) of Fluorodopa F 18 (F-DOPA) injection, but all had deficiencies. Other 6 publications did not include any information relevant to the confirmation of performance characteristic characteristics of F-DPOA and not relevant to the confirmation of efficacy or safety of F-DOPA.

Studies 15 & 16 are retrospective, single center, and with clinical diagnosis (after Parkinson's drug treatment response or non-response) as Standard of Truth (SOT) (lacking clinical utility).

Study # 15 was intended to validate the efficacy and safety of Fluorodopa F 18 PET as an imaging tool in the differential diagnosis of patients with parkinsonian symptoms. Clinical diagnosis information was provided by the referring physician. A protocol for study # 15 was not submitted to the Agency for review. The primary efficacy measure was visual assessment of PET Scan images by three qualified individuals as either positive (loss of dopaminergic neurons - demonstrated a reduced uptake of Fluorodopa F 18 Injection) or negative (no loss of dopaminergic neurons - showed a normal uptake of Flurodopa F 18), and a follow-up of 27 patients with negative F-18 FDOPA PET for 2-4 years (study 16) who were enrolled in the study #15.

The three blinded PET scan readers were also blinded to the physicians' diagnosis. There was no variability among three scan readers with regards to the visual assessment of the PET scans. For every one of the patients that were initially classified as "possible PD (Parkinson's Disease)", a positive PET scan result was recorded and for each patient that was initially classified as "possible non-PD", a negative PET scan result was recorded. For each healthy control subject, a negative PET scan result was recorded. There were no false positive or false negative scan results considering physician's clinical diagnosis as SOT, resulting in 100% sensitivity and 100% specificity for each reader.

Study # 16 had additional follow-up information on 27 out of a total of 185 patients. These patients had clinical diagnosis of suspected non-PD and were FDOPA scan negative patients. These patients were followed-up for 2-4 years and verified that none of these patients developed Parkinsonian syndrome - i.e. 2-4 year clinical follow-up as Standard of Truth (SOT) in FDOPA scan negative patients provides supplementary information to the clinical diagnosis. Other patients (FDOPA scan positive) were not followed-up.

Sponsor stated that Fluorodopa F 18 PET is not intended for screening patients for parkinsonian syndromes which are borderline cases. Since Parkinson's drug treatment has several side effects, an early detection based on the PET scan is important to avoid unwanted drug treatment for patients with parkinsonian syndromes, but no Parkinson's (or related) Disease. It appears that in about 15% of the cases where the physicians are in doubt, early detection using a PET scan is helpful to avoid unwanted treatment. These patients are likely to benefit as was seen in Study 15 (27/185 = 14.6%). However, these 15% patients with negative PD group were significantly younger than Normal group

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or Positive PD group and thus raising the question whether the difference in FDOPA PET results could largely be explained by age difference. Study # 15 was not properly designed to evaluate baseline differences.

Study # 21 is exploratory, single center with all study patients already diagnosed with PD (not the target patient population), and it is unclear how specificity and sensitivity were calculated.

The clinical data for efficacy and collective information submitted in this NDA including use of clinical diagnosis as SOT are not adequate to support an approval. The clinical value in terms of providing supplemental value to physician's clinical diagnosis is not provided. Therefore based on collective information and statistical analysis, a Complete Response is recommended due to lack of robust clinical data for efficacy and lack of follow-up for all patients. Feinstein Institute should continue using Fluorodopa F 18 Injection under an FDA approved Expanded Access IND (with a protocol and prospective analysis plan) and follow patients for at least 2 years to obtain outcome data which can be used as a standard of truth/reference.

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2. INTRODUCTION

Fluorodopa, also known as F-DOPA, is a fluorinated form of Levodopa (L-DOPA) primarily synthesized as its fluorine-18 isotopologue for use as a radiotracer in positron emission tomography (PET). Positron emission tomography (PET) is a nuclear medical imaging technique that produces a three-dimensional image or picture of functional processes in the body. PET technology using short-lived radioisotopes is a state of the art imaging technology.

Fluorodopa F 18 Injection belongs to the aromatic amino acid class of compounds. Once injected, Fluorodopa F 18 will cross the blood brain barrier to reach the striatal region where it undergoes decarboxylation to form fluorodopamine. As in the case of L-DOPA, the storage of the fluorodopamine in the striatum will depend upon the condition of the striatal region. Therefore, the storage of fluorodopamine F 18 in the striatum will depend upon the extent of neuronal loss. If the striatal region has no loss of dopaminergic neurons, Fluorodopa F 18 uptake in that region will be normal. However, if there is dopaminergic neuronal loss in the striatum, the uptake of fluorodopamine will be reduced depending upon the extent of the neuronal loss. According to the sponsor, (b) (4) Fluorodopa F 18 follows the same biological pathway as L-DOPA and the drug is excreted through the bladder in a similar way. The safety and effectiveness of L-DOPA is well established.

This radiotracer (F-DOPA) has already been approved by the European Union a long time back as a diagnostic imaging for the differential diagnosis of parkinsonian syndromes. Fluorodopa F 18 PET has been used for the last 20 years around the world.

2.1 Overview

The safety and efficacy of Fluorodopa F 18 Injection was presented by the FDA reviewers at the public meeting conducted by FDA on July 28, 2000. It was pointed out that the available literature data were insufficient to support efficacy in any patient population. A pre-IND meeting was held in 2008 and original NDA was submitted on 10/29/2009 with a PDUFA start date of 1/ 21/2010 (date user fee waiver granted). Refuse to File letter was issued on 3/19/2010.

This is a 505(b)(2) NDA re-submission/after refuse to file document number 19, and contains one clinical trial conducted by the applicant onsite, and the rest of the submission are from literature publications. This application is a substantial improvement over the original NDA submission which had no module 2 summaries and lack of integrated summary of efficacy (ISE) and integrated summary of safety (ISS) were cited as filing deficiencies in the RTF letter (3/19/2010). Information about ISE and ISS in this NDA is provided and individual summaries of several studies have been provided.

Feinstein Institute was approved by FDA to continue using Fluorodopa F 18 Injection under an Expanded Access IND on 6/21/2012. The current NDA was resubmitted on 10/22/2012.

2.1.1 Indication and Doses

Proposed indication: Fluorodopa F 18 Injection is a [redacted] (b) (4) used in Positron Emission Tomography (PET) to visualize dopaminergic [redacted] (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes (PS). [redacted] (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.

The proposed dosage form is injection. Strengths are 0.42mCi/mL to 8.33mCi/mL. Route of Administration is intravenous. At the Feinstein Institute, subjects were dosed with 150 mg of carbidopa one hour prior to administration of Fluorodopa F 18 Injection dose between 4-5mCi to generate a well resolved image. Fluorodopa F 18 is an imaging agent and is not for treatment purposes.

2.1.2 Identified Studies in the review

The sponsor provided reports of 9 Efficacy and Safety Studies (Studies #15-23). This included one 'controlled' study by the Applicant and reports of 8 publications.

The F-18 FDOPA PET efficacy data are derived from the following three studies.

Study # 15: **Clinical Study of Fluorodopa F 18 Injection Conducted by The Feinstein Institute for Medical Research:**

The Study # 15 is the primary clinical study conducted by the Feinstein Institute for Medical Research. The patient-level data were submitted to the NDA.

Study # 16: Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging:

Publication of a follow-up study on a subset of patients in Study #15 of F-18 FDOPA PET Negative Patients (27) published in a Journal "Movement Disord", 2007:22: 167-173 by Eckert, et al. – "Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging."

Study # 21: Direct Comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls – This paper reports results of a direct comparison of FP-CIT SPECT and F-DOPA PET in Patients with Parkinson's Disease and Healthy Controls. Report is based on the publication of an exploratory study comparing sensitivity and specificity of DaTscan and FDOPA.

Other studies are briefly mentioned below. For details, readers are referred to the clinical report.

Study # 17: **Striatal and Extrastriatal Dysfunction in Parkinson's Disease with Dementia: A 6-[^{18}F]Fluoro-L-Dopa PET Study**.

Publication of an exploratory study analyzing FDOPA influx constant (Ki) in various brain regions. With this study, the authors conclude a significant dysfunction in both the striatal and extrastriatal regions in patients with Parkinsonian syndromes. There was no information relevant to the confirmation of efficacy or safety of FDOPA in this paper.

Study # 18: A Comparison of the Progression of Early Parkinson's Disease in Patients Started on Ropinirole or L-Dopa: An 18F-Dopa PET Study.

Fluorodopa F 18 Injection was used to measure the progression of patients diagnosed with early-onset Parkinson's disease who had been treated with either ropinirole or levodopa. This was an exploratory study on disease progression (all patients were diagnosed with Parkinson Disease) and treatment response (to Ropinirole vs L-Dopa). The authors conclude that that after 2 years of treatment for patients with early parkinsonian syndromes, there is no significant difference in the rate of progression between patients started with ropinirole compared with L-dopa. The results were not related to the confirmation of efficacy or safety of FDOPA in this paper.

Study # 19: Slower Progression of Parkinson's Disease with Ropinirole versus Levodopa: The REAL-PET Study. Publication of a clinical study designed to compare treatment response to ropinirole vs. L-dopa; all patients recruited patients were already diagnosed with PD. This study was not designed to assess the diagnostic efficacy of FDOPA PET; and no relevant for confirmation of diagnostic performance characteristics of FDOPA included in this paper.

Study # 20: A Technique for Standardized Central Analysis of 6-Fluoro-L-Dopa PET from Multicenter Study. This study was a publication of technical portion of Study #19.

Study # 22: Simple Ratio Analysis (SOR) of ^{18}F-Fluorodopa Uptake in Striatal Subregions Separates Patients with Early Parkinson Disease from Healthy Controls –

The purpose of this study was to determine whether a simple ratio analysis and K_i values calculated from the PET scans of the PD patients demonstrate a definite difference from those values obtained for the healthy normal subjects. The authors conclude that a single 15 minute scan 75 minutes post injection of Fluorodopa F 18 will provide well resolved images to detect dopaminergic deficit. The paper does not provide any relevant information for confirmation of diagnostic performance characteristics of FDOPA

Study # 23: Fluorine-18-Fluoro-L-DOPA Dosimetry with Carbidopa Pretreatment.

The purpose of this study was to determine the absorbed radiation dose in various organs in human subjects after the administration of Fluorodopa F 18 Injection. The study also determined the effective dose as a means of characterizing the biologic significance of radiation dose. A total of 23 subjects were included in this study. The results are based on publication of an exploratory study showing the effect of carbidopa pretreatment on FDOPA biodistribution and dosimetry. (clinpharm study no efficacy or safety discussed)

Reference ID: 3329478

2.2 Data Sources

Electronic datasets were not submitted. The applicant was requested to submit datasets (patient level information) to allow substantive review to occur. On 12/17/2012, the applicant submitted patient level data, patient consent form, patient data collection sheet (sample case report form), study protocol, statistical analysis. The data were submitted in Excel format.

The NDA in eCTD located at: \\CDSESUB4\NONECTD\NDA200655\5168335

3. STATISTICAL EVALUATION

There were three studies for the efficacy analysis, namely sponsor's study numbers 15, 16 and 21. These studies are the main focus of this review. The sponsor also provided additional information on several studies based on publications, as mentioned above.

3.1 Data and Analysis Quality

There were two studies listed as controlled clinical studies (both conducted in the U.S.), including one conducted by the applicant (Feinstein Inst.) on site (study # 15), and the other, a publication of a follow-up study of a subset of patients in the onsite Feinstein study (study # 16). Since the applicant conducted both pivotal studies, the applicant was requested to submit datasets (patient level information) to allow substantive review to occur. On 12/17/2012, the applicant submitted patient level data, patient consent form, patient data collection sheet (sample case report form), study protocol, statistical analysis, and a cover letter as an amendment to the NDA. The deficiency regarding the lack of ISE and ISS was also resolved. During the course of statistical review, some additional information was also requested which the sponsor promptly provided.

3.2 Evaluation of Efficacy

3.2.1 Study Design

Study # 15: This is the primary retrospective single center study conducted by the Feinstein Institute for Medical Research. A protocol for this study was not submitted to the Agency for review. This study was intended to validate the efficacy and safety of Fluorodopa F 18 PET as an imaging tool in the differential diagnosis of patients with parkinsonian symptoms. In this study, two groups of patients were used. Normal subjects were also included in the study for comparison. Clinical diagnosis information was provided by the referring physician. Clinical diagnosis was based on the United Parkinson's Disease Rating Scale (UPDRS) and physical examination of the patient. No other diagnostic testing was used for the assessment of the clinical symptoms.

Based on the physician's clinical diagnosis, the patient was referred to the Feinstein Institute medical center for a Fluorodopa F 18 PET scan. A patient was deemed eligible for the study only if they showed at least two cardinal symptoms of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). This was the primary criteria for patient inclusion. Study Drug Dosing was 4-5 mCi intravenous. Patient preparation: subjects were dosed with 150 mg of carbidopa one hour prior to administration of Fluorodopa F 18 Injection dose between 4-5mCi to generate a well resolved image.

PET Scan was performed. Images (PET Scan) were interpreted visually by three qualified individuals as either positive (loss of dopaminergic neurons - demonstrated a reduced uptake of Fluorodopa F 18 Injection) or negative (no loss of dopaminergic neurons - showed a normal uptake of Flurodopa F 18). The image readers were blinded to the clinical diagnosis information provided by the referring physician. The readers were also blinded to the striatal occipital ratio (SOR) calculation which was used to further

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confirm the image interpretation. There was a defined inclusion criteria, and image interpretation by blinded readers. These readings were compared and the diagnostic accuracy was evaluated. A report was generated based on the assessment of the scan and the results were conveyed to the referring physician.

Study # 16: This study is a follow-up of F-18 FDOPA PET Negative Patients (27) from study # 15 published in a Journal "Movement Disord", 2007:22: 167-173 by Eckert, et al. – "Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging"

3.2.2 Objective

The primary objective was to assess loss or no loss of dopaminergic neurons in the striatum of adult patients with suspected Parkinsonian syndromes (PS).

3.2.3 Primary Criteria for evaluation

The primary efficacy measure was visual assessment of PET Scan images by three qualified individuals as either positive (loss of dopaminergic neurons - demonstrated a reduced uptake of Fluorodopa F 18 Injection) or negative (no loss of dopaminergic neurons - showed a normal uptake of Flurodopa F 18), and a follow-up of 27 patients with negative F-18 FDOPA PET for 2-4 years (study 16) who were enrolled in the study #15.

3.2.4 Demographic and Baseline Characteristics

The study population for efficacy in Study 15 includes 196 adults. The characteristics of subjects according to study group are given in the following Table 1.

Table 1: Characteristics of Subjects According to Study Group
(mean ± SD (median; minimum-maximum) or n (%))

Characteristic	NEG-PD (n=27)	NORMALS (n=11)	POS-PD (n=158)
Age (years)	45.3 ± 19.3 (42; 17-86)	58.6 ± 15.2 (68; 34-72)	56.8 ± 12.5 (54.5; 16-81)
% Male	16/27 (59.3%)	8/11 (72.7%)	91/158 (57.6%)

Negative PD group was younger than Normal group or Positive PD group. There was no statistically significant difference in gender distribution across the three patient groups.

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The details are provided in Tables 2 and 3.

Table 2: Age Category versus Clinical Diagnosis

	Clinical Diagnosis			
Age Category	Normal	PD	Suspected non-PD*	Total
<= 20 n (%)	0 (0)	1 (0.6)	1 (3.7)	2
21-45 n (%)	3 (27.3)	22 (13.9)	14 (51.9)	39
46-70 n (%)	6 (54.6)	103 (65.2)	7 (25.9)	117
>70 n (%)	2 (5.1)	32 (16.3)	5 (18.5)	39
Total	11	158	27	196

Table 3: Gender versus Clinical Diagnosis

	Clinical Diagnosis			
Gender	Normal	PD	Suspected non-PD*	Total
Female n (%)	3 (27.3)	67 (42.4)	11 (40.7)	81 (41.3)
Male n (%)	8 (72.7)	91 (57.6)	16 (59.3)	115 (58.7)
Total	11	158	27	196

Note: Since patients were only followed-up for FDOPA scan negative patients for 2-4 years and verified that none of these patients developed Parkinsonian syndrome - i.e. 2-4 year clinical follow-up as Standard of Truth (SOT) in FDOPA scan negative patients, the negative predictive value for these patients in each age group or for each gender is 100% using SOT.

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3.3 Results and Conclusions

3.3.1 Study # 15

The primary endpoint is the visualization of the striatal region using Fluorodopa F 18 PET as a biomarker. Sponsor states that (b) (4) A reduced uptake of Fluorodopa F 18 due to neuronal loss will reduce the size and shape of the putamen and caudate (crescent shape structure) depending upon the disease severity. If there is no loss of neurons, the PET scan will be normal (full crescent shaped structure). These two conditions will be clearly demonstrated in the PET scan and the results are interpreted as positive (loss of dopaminergic neurons) or negative (no loss of dopaminergic neurons). This is the pre- specified event by which the efficacy is established.

A total of 185 patients were referred by movement disorder specialists and classified as either "possible-PD" or "possible-non PD" based on their symptoms and response to typical Parkinon's disease treatment.

In addition to the patient population, eleven healthy normal controls were included in the study.

Subjects were dosed with 150 mg of carbidopa one hour prior to administration of Fluorodopa F 18 Injection (4-5 mCi).

A visual examination of each subjects PET scan by three separate blinded readers resulted in 27 of the 185 patients (15%) being classified as having no loss of dopaminergic neurons. A Striatal Occipital Ratio (SOR) quantification of these patients revealed normal SOR values (Mean = 2.4781; SD= 0.1559) which were same as the SOR values calculated for the normal healthy controls (Mean = 2.5452; SD = 0.1297).

The remaining 158 patients were classified by visual assessment of the PET scan as having a loss of dopaminergic neurons. The SOR values for this group of patients (Mean = 1.6854: SD = 0.1232) were much lower than the SOR values of normal subjects or those patients with no dopaminergic loss.

There was no variability among scan readers with regards to the visual assessment of the PET scans. The three blinded PET scan readers were also blinded to the physicians' diagnosis. For every one of the patients that were initially classified as "possible PD", a positive PET scan result was recorded and for each patient that was initially classified as "possible non-PD", a negative PET scan result was recorded. For each healthy control subject, a negative PET scan result was recorded. There were no false positive or false negative scan results considering physician's clinical diagnosis as SOT, resulting in 100% sensitivity and 100% specificity.

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3.3.2 Study # 16

This study # 16 is a continuation of the clinical study # 15 conducted by The Feinstein Institute for Medical Research to further evaluate the patients that exhibited parkinsonian symptoms but had normal dopaminergic imaging. There were 27 patients with negative F-18 FDOPA PET and these patients were followed for 2-4 years. The results were published in a Journal "Movement Disord", 2007:22: 167-173 by Eckert, et al. – "Regional Metabolic Changes in Parkinsonian Patients with Normal Dopaminergic Imaging." These patients were referred by a movement disorder physician and exhibited at least two of the cardinal features of parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder. They ("suspected non-PD") were referred due to the nonresponse of the patient to typical Parkinson's disease treatment.

3.3.3 Integrated Results of Study # 15 and # 16

Table 4 summarizes PET scan results versus clinical diagnosis for two studies (# 15 and # 16).

Table 4: PET Scan Results versus Clinical Diagnosis

	Clinical Diagnosis			
PET Scan Results	Normal	PD	Suspected non-PD*	Total
Normal (n)	11	0	27	38
Positive (n)	0	158	0	158
Total (n)	11	158	27	196

*All confirmed by follow-up (SOT) - Feinstein only followed FDOPA scan negative patients for 2 to 4 years clinical follow-up past the study date as SOT and verified that none of these patients developed Parkinsonian syndrome.

3.3.4 Study # 21: Comparison of FP-CIT SPECT and F-DOPA PET

I-123 FP-CIT SPECT (DaTscan) is approved in the U.S. and Europe. It selectively binds to dopamine transporter (DaT) => DaT imaging agent. It is indicated for striatal dopamine transporter visualization by SPECT brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian syndromes (PS). In these patients, DaTscan may be used to help differentiate essential tremor from tremor due to Parkinsonian Syndrome (idiopathic Parkinson's disease, multiple system atrophy and progressive supranuclear palsy). Recommended dosing is 111 to 185 MBq (3 to 5 mCi).

F-18 FDOPA PET vs. I-123 DaTscan SPECT

The effectiveness of FP-CIT SPECT imaging versus F-DOPA PET imaging in patients with Parkinson's disease was directly compared in this study using a patient population with strong

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clinical evidence of having Parkinson's disease. Healthy controls in a similar age range as the patients were also used in this study.

This was a single center study in Europe. The inclusion criteria: patients with strong clinical evidence of having Parkinson's disease. The exclusion criteria: patients with atypical signs, psychiatric disorders, signs of severe cognitive deterioration, severe cardiovascular co-morbidity or on medication known to interfere with dopamine transporters (DaT) or catechol-O-methyltransferase inhibitors. The study drug dosing was 1> 2.5 mg/kg carbidopa PO 1 hour prior to FDOPA 2> 200 MBq F-18 FDOPA IV 3> 185 MBq DaTscan IV.

A total of 29 patients were recruited. The Standard of Truth (SOT): all patients were followed for 1 year after the scans. This resulted in 28 patients included in the analysis (One patient was excluded). Each of the 28 patients had both FDOPA PET and DaTscan SPECT in order to compare the relative efficacies of both radiotracers.

There were 11early-stage patients who had strong clinical evidence of PD based on two of the three cardinal symptoms (rest tremor, bradykinesia and rigidity), disease duration of less than 3 years, and were not using antiparkinson medication.

There were 17 advanced-stage patients who had two of the three cardinal symptoms, disease duration of 5–15 years, and were using antiparkinson medication with a documented response.

There were 20 controls (10 FDOPA + 10 DaTscan).

3.3.5 Results of Study # 21

The patients' demographics for the Study # 21 are given in Table 5. This table shows that early-stage patients were younger than controls and controls were younger than advanced PD patients. The age of patients with advanced disease was higher than the age of patients with early-stage disease.

Table 5: Patients Demographics for Study # 21

	Controls		Early-stage patients		Advanced-stage patients	
	FP-CIT	F-DOPA	FP-CIT	F-DOPA	FP-CIT	F-DOPA
No. of Subjects	10	10	11	11	17	17
Men	5	5	8	8	15	15
Women	5	5	3	3	2	2
Age (years)						
Mean	60.2	61.4	51.3	51.3	64.5	64.5
Standard Deviation	8.7	8.5	10.1	10.1	6.3	6.3

Reproduced from publication

The Sensitivity and specificity were calculated and were based on uptake values for each brain region – contralat/ipsilat putamen, caudate, striatum. A methodology for determining the standard of truth, sensitivity and specificity was not clear in the published paper and the data were not

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provided. This reviewer could not reproduce results based on the limited summary data provided in the published report. Therefore the results as given in the published paper are reproduced in Table 6 for sensitivity and specificity for DaTscan & F-DOPA for Study # 21.

Table 6: Results for Sensitivity & Specificity for DaTscan & F-DOPA for Study # 21

Brain Regions	Sensitivity (DaTscan)	Sensitivity (F-DOPA)	Specificity (DaTscan)	Specificity (F-DOPA)
All Patients				
Contralateral Putamen	100	100	90	96
Ipsilateral Putamen	100	91	90	86
Ipsilateral Caudate	91	91	100	100
Contralateral Caudate	82	64	100	89
Contralateral Striatum	100	100	100	100
Ipsilateral Striatum	73	82	90	93
Early Stage Patients				
Contralateral Putamen	91	91	100	90
Ipsilateral Putamen	82	64	90	90
Ipsilateral Caudate	100	100	100	100
Contralateral Caudate	100	91	100	90
Contralateral Striatum	100	100	100	100
Ipsilateral Striatum	73	82	100	90

Reproduced from publication - Comparable Sensitivity & Specificity between DaTscan and FDOPA

3.4 Evaluation of Safety

Applicant did not submit any safety data in the NDA. Applicant states that ^{18}F is a short-lived radioisotope, at the end of the study there is only trace amounts of radiation left in the brain and the patient has minimal radiation risk. There were no adverse events after the administration of Fluorodopa F 18 and there was no premature discontinuation from the study due to complication. There have been no safety concerns from over 20 years of use of the drug at the Feinstein Institute. This is a derivative of L-dopa, which has a known safety profile.

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

For the study # 15, findings were assessed for each of the primary variables by gender and age. The results indicated a general consistency across each stratification for each reader. There was no difference in the efficacy data obtained from the male and female group of patients either in the published data.

Since Fluorodopa F 18 is used in different regions around the world, the subject population includes people with a wide range of ethnic backgrounds. Males and females of various ages, heights and weights were also included. According to the applicant, there is no indication that the drug behaves differently in any specific subpopulation. There were no observable differences in the PET images among subjects due to any type of characteristic other than disease state. As no adverse events have been reported, there is also no indication that Fluorodopa F 18 Injection would pose a risk to any subpopulation.

4.2 Other Special/Subgroup Populations

There were no special subgroups or populations identified by the clinical team for analyses in this review.

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

There were two relevant clinical studies – one conducted by applicant (study # 15) with a follow-up of 27 scan negative patients (study # 16). These studies had several deficiencies:

- They were single center retrospective studies. A protocol was not submitted for review to the Agency. There were design issues in the study, especially borderline cases of patients with very mild symptoms of parkinsonian syndromes were not fully evaluated. Patients with at least two cardinal symptoms of parkinsonian syndromes were included in the study.
- Study drug lacks clinical utility if patient's diagnosis is already clear. For patients who were *suspected* of Parkinson Disease, there is no further follow-up of most patients to confirm patient's clinical diagnosis (only patients with negative FDOPA PET were followed).
- Although 27 FDOPA PET negative patients were followed for ≥ 2 year to obtain patient's true clinical diagnosis, there is age difference between FDOPA PET positive patients and FDOPA PET negative patients raising the question whether the difference in FDOPA PET results could largely be explained by age difference.

Sponsor's supportive study # 21 is a direct comparison of FP-CIT SPECT and F-DOPA PET in patients with Parkinson's Disease and Healthy Controls. The results are based on the publication of an exploratory study comparing sensitivity and specificity of DaTscan and FDOPA. This study also has following limitations:

- It is a single center study, data were not provided and the methodology used is not clear. The results could not be verified.
- All study patients had strong clinical evidence of PD, and these patients may not need another imaging test to confirm diagnosis.
- Patients with atypical symptoms were excluded, but these are patients who may benefit from an imaging test in further diagnostic work-up.

5.2 Conclusions and Recommendations

Information on 9 studies was submitted. All these studies are post-hoc evaluation including primary clinical study # 15 conducted by the sponsor. Eight (8) out of 9 studies are from literature publications. Three (3) out of 9 studies were found relevant for evaluating diagnostic efficacy (performance characteristics) of Fluorodopa F 18 (F-DOPA) injection, but all had serious deficiencies. Other 6 publications did not include any information relevant to the confirmation of performance characteristic characteristics of F-DPOA and not relevant to the confirmation of efficacy or safety of F-DOPA.

Studies 15 & 16 are retrospective, single center, and with clinical diagnosis as Standard of Truth (SOT).

Study # 15 was intended to validate the efficacy and safety of Fluorodopa F 18 PET as an imaging tool in the differential diagnosis of patients with parkinsonian symptoms. Clinical diagnosis

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information was provided by the referring physician. A protocol for study # 15 was not submitted to the Agency for review. The primary efficacy measure was visual assessment of PET Scan images by three qualified individuals as either positive (loss of dopaminergic neurons - demonstrated a reduced uptake of Fluorodopa F 18 Injection) or negative (no loss of dopaminergic neurons - showed a normal uptake of Flurodopa F 18), and a follow-up of 27 patients with negative F-18 FDOPA PET for 2-4 years (study 16) who were enrolled in the study #15.

There was no variability among three scan readers with regards to the visual assessment of the PET scans. The three blinded PET scan readers were also blinded to the physicians' diagnosis. For every one of the patients that were initially classified as "possible PD (Parkinson's Disease)", a positive PET scan result was recorded and for each patient that was initially classified as "possible non-PD", a negative PET scan result was recorded. For each healthy control subject, a negative PET scan result was recorded. There were no false positive or false negative scan results considering physician's clinical diagnosis as SOT, resulting in 100% sensitivity and 100% specificity for each reader.

Study # 16 had additional follow-up information on 27 out of a total of 185 patients. These patients had clinical diagnosis of suspected non-PD and were FDOPA scan negative patients. These patients were followed-up for 2-4 years and verified that none of these patients developed Parkinsonian syndrome - i.e. 2-4 year clinical follow-up as Standard of Truth (SOT) in FDOPA scan negative patients provides supplementary information to the clinical diagnosis. Other patients (FDOPA scan positive) were not followed-up.

Sponsor stated that Fluorodopa F 18 PET is not intended for screening patients for parkinsonian syndromes which are borderline cases. Since Parkinson's drug treatment has several side effects, an early detection based on the PET scan is important to avoid unwanted drug treatment for patients with parkinsonian syndromes, but no Parkinson's (or related) Disease. It appears that in about 15% of the cases where the physicians are in doubt, early detection using a PET scan is helpful to avoid unwanted treatment. These patients are likely to benefit as was seen in Study 15 (27/185 = 14.6%). However, these 15% patients with negative PD group were significantly younger than Normal group or Positive PD group and thus raising the question whether the difference in FDOPA PET results could largely be explained by age difference. Study # 15 was not properly designed to evaluate baseline differences.

The clinical data for efficacy and collective information submitted in this NDA including use of clinical diagnosis as SOT are not adequate to support an approval. The clinical value in terms of providing supplemental value to physician's clinical diagnosis is not provided. Therefore based on collective information and statistical analysis, a Complete Response is recommended due to lack of robust clinical data for efficacy and lack of follow-up for all patients. Feinstein Institute should continue using Fluorodopa F 18 Injection under an FDA approved Expanded Access IND and follow 20-30 patients for at least 2 years to obtain a standard of truth/reference.

SIGNATURES/DISTRIBUTION LIST

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Primary Statistical Reviewer: Satish C. Misra, Ph. D.
Date: June 3, 2013

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/s/

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06/21/2013

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06/23/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science (OTS)
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

MEMORANDUM

NDA/Serial Number:	200-655 (b) (4)
Drug Name:	Flurodopa F 18 injection
Indication(s):	PET Imaging drug Flurodopa F 18 injection
Applicant:	Feinstein Institute via Thomas Chaly, Ph.D.
Date(s):	Submit Date: 16 June 2010 Receive Date: 17 June 2010
Review Priority:	Type B Meeting Date: July 19, 2010
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Satish C. Misra, Ph. D.
Concurring Reviewers:	Jyoti Zalkikar, Ph. D.
Medical Division:	Division of Medical Imaging Products (DMIP)
Clinical Team:	Brenda Ye, M. D
Project Manager:	Frank A Lutterodt

Keywords: Sensitivity, Specificity, Imaging, Safety, Efficacy

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/s/

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10/26/2010

JYOTI ZALKIKAR
11/04/2010

Clinical Pharmacology Review	
NDA	200-655; SDN 37 and 43
Submission Date	December 15, 2015 and February 25, 2016
Brand Name	Fluorodopa F18 Injection
OCP Reviewer	Christy S John, Ph.D.
OCP Team Leader	Gene M. Williams, Ph.D.
OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Medical Imaging Products
Applicant	Feinstein Institute of Medical Research
Submission Type	Original-1 (Type 1- New Molecular Entity); Resubmission/Class 2
Dosing regimen	The proposed dose for an adult is (b) (4) 5.0 mCi ((b) (4) 0.185GBq).
Indication	(b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic investigations.

Reference ID: 3916903

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Reference ID: 3916903

1 EXECUTIVE SUMMARY

The applicant has re-submitted NDA 200655 for Fluorodopa F18 Injection in response to the complete response letter the Agency issued on October 22, 2013. The major issues identified in FDA's complete response letter were clinical, product quality and manufacturing facilities. The original submission was acceptable from a clinical pharmacology perspective and no post-marketing requirements or commitments were recommended.

This re-submission contains only one additional clinical study, Study 17. Study 17 used Fluorodopa F18 PET scans to differentiate between Parkinsonism (Idiopathic Parkinson's Disease and Progressive Supranuclear Palsy) and non-Parkinsonism [e.g., Essential Tremors, Dopamine Responsive Dystonia, and SWEDD (scan without dopaminergic deficit)]. Patients with essential tremor are expected to have normal (negative) PET scans. The studied dose was 4.05 - 5 mCi of Fluorodopa, which is not significantly different than that used in the clinical study submitted in the original NDA (Study 15).

The primary end point for Study 17 was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." "Loss" of dopaminergic neurons in the striatum was based upon the reader's judgment of what a "no loss" image looks like, not upon a prior scan in the same patient. The sensitivity of fluorodopa F18 injection, defined as "loss" of dopaminergic neurons in the striatum of patients having a clinical diagnosis of Parkinson's, was 100%. Specificity could not be determined as 7 of 13 scan negative (i.e., "no loss") patients did not have Standard of Truth (SoT).

The applicant collected Striatal-Occipital Ratio (SOR) in Study 17. Striatal Occipital Ratio is the ratio of radioactivity in the striatum (target) to that of the occipital cortex (background). These SOR values were not used for the visual interpretation of the PET scan results. The reviewer's analysis of the data shows that, on average, SOR differed as a function of disease. However, because there was considerable overlap between SORs in patients with Parkinson's and healthy subjects, SOR cannot be used as an aid to scan interpretation.

The applicant's proposed dose for the package insert is (b) (4) 5.0 mCi. However, Study 17 used a dose of 4.05-5 mCi. There is no basis for using a dose range and there is a potential for an unclear scan if the dose is too low. We recommend a dose of 5 mCi.

The current submission has no new information on metabolism, drug interactions, or specific populations. The following (indented) is reproduced from the review of the original NDA.

> "No drug interaction studies have been reported in literature. However, it is not known whether drugs that are used to treat Parkinsonian syndromes can alter the disposition of Fluorodopamine F18 or the accumulation/retention of 18F in the striatum or rest of the brain. For this reason, the applicant's clinical trials required patients to discontinue any Parkinsonian medications at least 12 hours prior to the PET study. The proposed package insert includes this restriction. No special population studies or organ impairment studies have been reported."

1.1 Recommendations

From a clinical pharmacology perspective, we recommend approval of NDA 200-655 based on 100% sensitivity in detecting loss of dopaminergic neurons in the striatum of patients clinically diagnosed with Parkinson's Disease in Study 17†.

Decision	Acceptable to OCP?			Comment
Overall	Yes ☒	No ☐	NA ☐	
Evidence of Effectiveness†	Yes ☒	No ☐	NA ☐	Study 17
Proposed dose for general population	Yes ☒	No ☐	NA ☐	The applicant proposed dose is (b) (4) 5.0 mCi. The reviewer recommends the dose used in the new clinical trial (5.0 mCi)
Proposed dose selection for others	Yes ☐	No ☐	NA ☒	No basis for dose adjustment
Labeling	Yes ☐	No ☒	NA ☐	Revised labeling is proposed

†This decision is from a clinical pharmacology perspective only. The determination of the overall safety and effectiveness is made by the clinical review team.

Labeling Recommendations

Refer to Section **3 DETAILED LABELING RECOMMENDATIONS**.

1.2 Post-Marketing Requirements and Commitments

No post-marketing requirements or commitments are recommended.

SIGNATURES

Reviewer: Christy S John, Ph.D. Division of Clinical Pharmacology V	Team Leader: Gene Williams, Ph.D. Division of Clinical Pharmacology V
Division Director: Nam Atiqur Rahman, Ph.D. Division of Clinical Pharmacology V	

Cc: DMIP: PM T. Nguyen; MTL A. Gorovets; MO B. Ye
DCPV: Reviewer C. John; TL G. Williams; DDD B. Booth; DD A. Rahman

An Office of Clinical Pharmacology (OCP) Briefing was held for the review of the original NDA on June 12, 2013.

1.3 Summary of Clinical Pharmacology Findings

This re-submission contains only one additional clinical study, Study 17. Study 17 used Fluorodopa F18 PET scans to differentiate between Parkinsonism (Idiopathic Parkinson's Disease and Progressive Supranuclear Palsy) and non-Parkinsonism [e.g., Essential Tremors, Dopamine Responsive Dystonia, and SWEDD (scan without dopaminergic deficit)]. Patients with essential tremor are expected to have normal (negative) PET scans.

The studied dose was 4.05 - 5 mCi of Fluorodopa, which is not significantly different than that used in the clinical study submitted in the original NDA (Study 15).

The primary end point for Study 17 was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." "Loss" of dopaminergic neurons in the striatum was based upon the reader's judgment of what a "no loss" image looks like, not upon a prior scan in the same patient. The sensitivity of fluorodopa F18 injection, defined as "loss" of dopaminergic neurons in the striatum of patients having a clinical diagnosis of Parkinson's, was 100%. Specificity could not be determined as 7 of 13 scan negative (i.e., "no loss") patients did not have Standard of Truth (SoT).

The applicant collected Striatal-Occipital Ratio (SOR) in Study 17. Striatal Occipital Ratio is the ratio of radioactivity in the striatum (target) to that of the occipital cortex (background). These SOR values were not used for the visual interpretation of the PET scan results. The reviewer's analysis of the data shows that, on average, SOR differed as a function of disease. However, because there was considerable overlap between SORs in patients with Parkinson's and healthy volunteers, SOR cannot be used as an aid to scan interpretation.

The applicant's proposed dose for the package insert is (b) (4) 5.0 mCi. However, Study 17 used a dose of 4.05-5 mCi. There is no basis for using a dose range and there is a potential for an unclear scan if the dose is too low. We recommend a dose of 5 mCi.

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

See clinical pharmacology review of original NDA 200-655 (**Appendix 4.2** of this review).

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

This NDA re-submission contains only one additional clinical study (Study #17). 4.05 - 5 mCi of Fluorordopa was administered to patients intravenously. The "cold" mass dose associated with

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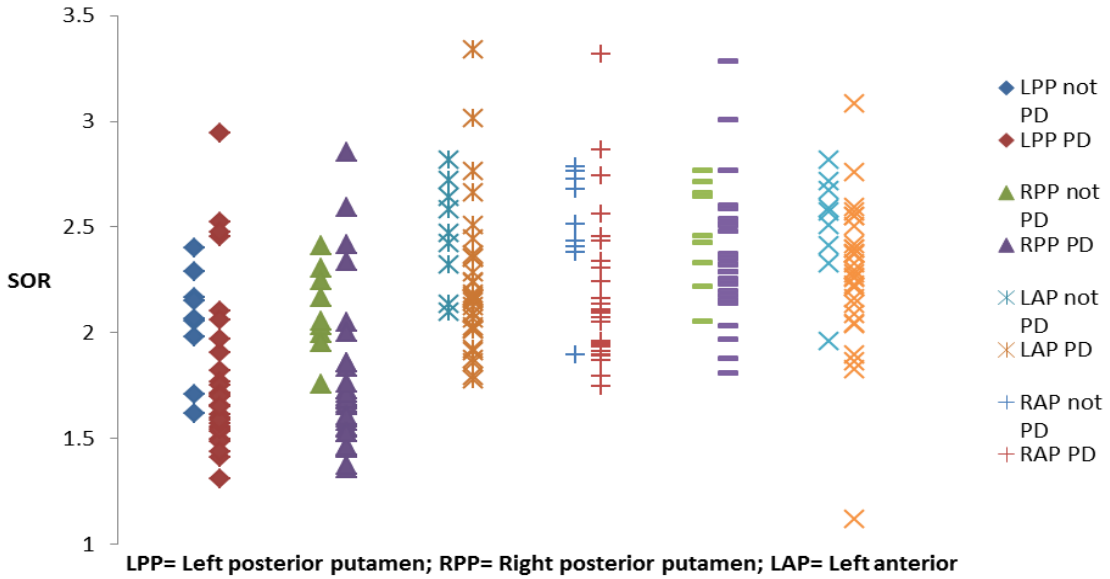
this radioactive dose is [redacted] (b) (4) mg. 150 mg of carbidopa was administered orally to patients 60-90 minutes prior of Flurodopa 18 injection. These doses are not significantly different than those in the clinical study submitted in the original NDA, which was approvable from a clinical pharmacology perspective.

The applicant's proposed dose for the package insert is [redacted] (b) (4) 5.0 mCi. However, Study 17 used a dose of 4.05-5 mCi. There is no basis for using a dose range. We recommend a dose of 5 mCi.

PET scans were evaluated by three different readers. Patients were followed up to two years following PET scan a clinical diagnosis was used as a Standard-of-Truth (SoT). The primary end point for Study 17 was the visualization of dopaminergic neurons in the striatum expressed as a binary variable: "loss" / "no loss." "Loss" of dopaminergic neurons in the striatum was based upon the reader's judgment of what a "no loss" image looks like, not upon a prior scan in the same patient. The sensitivity of fluorodopa F18 injection, defined as "loss" of dopaminergic neurons in the striatum in patients having a clinical diagnosis of Parkinson's, was 100%. Specificity could not be determined as 7 of 13 scan negative (i.e., "no loss") patients did not have Standard of Truth (SoT).

The applicant collected quantitative data (Striatal-Occipital Ratio: SOR) during the study. These SOR values were not used for the visual interpretation of the PET scan results. The applicant provided no analysis of the SOR data. The reviewer's plot of the data is shown as **Figure 1**. The data show that SOR did not differ as a function of disease. Thus, there is not potential to use SOR as an aid to scan interpretation.

Figure 1. Striatal-Occipital Ratio (SOR) by Striatal Brain Region and Standard-of-Truth (SoT; based on clinical diagnosis)



LPP= Left posterior putamen; RPP= Right posterior putamen; LAP= Left anterior putamen; RAP= Right anterior putamen; LC= Left caudate; RC= Right caudate PD= Parkinson's disease; not PD= not Parkinson's disease

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD) and how are they measured in clinical pharmacology and clinical studies?

Striatal-Occipital ratio was selected as an endpoint because the occipital cortex has limited dopaminergic innervation. The lack of dopaminergic nerve terminals that project to the occipital cortex makes it an appropriate control tissue for background.

2.3 INTRINSIC FACTORS

2.3.1 Do intrinsic factors (race, gender, age, body weight, tumor type, genetic polymorphisms, renal function, and hepatic function) influence the PK and are dose adjustments needed based on these intrinsic factors?

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

The clinical pharmacology review of original NDA 200-655 (**Appendix 4.2** of this review) did not identify a basis for dose adjustments. Study 17 provides no data that could be used to make dose adjustment recommendations.

2.2 EXTRINSIC FACTORS

See clinical pharmacology review of original NDA 200-655 (**Appendix 4.2** of this review).

2.5 GENERAL BIOPHARMACEUTICS

See clinical pharmacology review of original NDA 200-655 (**Appendix 4.2** of this review).

2.6 ANALYTICAL SECTION

Pharmacokinetics were not performed in Study 17.

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3 DETAILED LABELING RECOMMENDATIONS

The applicant's proposed package insert is attached to this review as **Appendix 4.1**. Internal labeling meetings have yet to occur. The following changes are anticipated.

Section **7 DRUG INTERACTIONS**

Delete section.

Section **12.2 Pharmacodynamics**

Applicant to provide data that optimal imaging occurs 75 – 90 minutes post-dosing or delete current PI language.

Section **12.3 Pharamcokinetics** Distribution

Applicant to provide data on the time course of distribution to non-CNS tissue or change proposed PI language.

Information on concomitant dosing of carbidopa to be moved to **2 DOSAGE AND ADMINISTRATION**

Section **12.3 Pharamcokinetics** Metabolism

Applicant to provide a quantitative description (what fraction of administered drug mass or radioactivity goes via each route identified) of how FDOPA is metabolized systemically or change proposed PI language.

Section (b) (4) **12.3 Pharamcokinetics** Elimination.

Applicant to provide data on time course of excretion via urine.

Advising patient to void moved to sections **2 DOSAGE AND ADMINISTRATION** and **17 PATIENT COUNSELING INFORMATION.**

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4 APPENDICES

4.1 APPLICANT'S PROPOSED PACKAGE INSERT

4.2 CLINICAL PHARMACOLOGY REVIEW OF ORIGINAL NDA 200-655

4.3 OCP FILING FORM

4.1 APPLICANT'S PROPOSED PACKAGE INSERT

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2 CLINICAL PHARMACOLOGY REVIEW OF ORIGINAL NDA 200-655

Clinical Pharmacology Review

NDA	200-655
Submission Dates	October 22, 2012, SDN 19
Type/Category	Original-1 (Type 1- New Molecular Entity); Resubmission/After Refusal to File
Brand Name	Fluorodopa F 18 Injection
Generic Name	Fluorodopa F 18 Injection
Proposed Indication	Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET**)** to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.
Dose	(b) (4) 5.0 mCi ((b) (4) 0.185GBq)
Route of Administration	Intravenous
Applicant	Feinstein Institute for Medical Research (FIMR)
Reviewing Division	Division of Clinical Pharmacology 5 (DCP 5)
Medical Division	Division of Medical Imaging Products (DMIP)
Primary Reviewer	Christy S. John, Ph.D.
Secondary Reviewer	Gene Williams, Ph.D.

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4.1. Applicant's Proposed Package Insert (original, annotated)	
4.2. Cover sheet and OCPB Filing/Review Form	

Reference ID: 3926908

1. Executive Summary

The applicant, Feinstein Institute of Medical Research (FIMR), has resubmitted (after a refusal to file in March 2010) NDA (200-655) for Flurodopa F 18 Injection as a diagnostic PET (Positron Emission Tomography) imaging "to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations."

This application is supported by literature data along with one clinical trial conducted by the applicant. There was 100% correlation between the visual assessment of the PET images and the clinical diagnoses.

The proposed dose is an intravenous injection of (b) (4) 5 mCi. The selection of dose was based on the applicant's review of literature prior to conducting their study. The applicant used a dose of 4-5 mCi for their pivotal clinical trial. The "cold" mass dose associated with this radioactive dose is (b) (4) mg.

The primary information for clinical pharmacology review for this submission is derived from fourteen published literature submitted by the applicant. No clinical pharmacology studies were conducted by FIMR.

Fluorodopa F 18 undergoes decarboxylation by the enzyme aromatic amino acid decarboxylase (AAAD) to produce Fluorodopamine F 18. In order to decrease decarboxylation by AAAD, and increase bioavailability to the brain, patients are pretreated with carbidopa, an inhibitor of AAAD. The applicant selected the carbidopa dose of 150 mg based on their assessment of peer-reviewed publications.

No drug interaction studies have been reported in literature. However, it is not known whether drugs that are used to treat Parkinsonian syndromes can alter the disposition of Fluorodopamine F 18 or the accumulation/retention of ^{18}F in the striatum or rest of the brain. For this reason, the applicant's clinical trials required patients to discontinue any Parkinsonian medications at least 12 hours prior to the PET study. The proposed package insert includes this restriction.

No special population studies or organ impairment studies have been reported.

1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5, has reviewed the submission NDA 203-155. The application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached in labeling.

1.2. Phase 4 Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments.

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1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

FIMR conducted a clinical trial to support the efficacy of Fluorodopa F 18 injection for PET imaging for the determination of the loss of functional dopaminergic neurons. All patients in the study were referred to FIMR by a movement disorder physician and exhibited at least two of the cardinal features of Parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). Patients entered the study with a classification of "Parkinson's Disease (PD) suspected" or "PD not suspected" from the movement disorder specialist. This clinical diagnosis by the movement disorder specialist was the standard of truth for interpretation of the PET scan results. There was 100% correlation between the visual assessment of the PET images and the clinical diagnoses. The clinical efficacy results are summarized in Table 1.

FDA Table 1. Clinical Efficacy Results

	Clinical Diagnosis		
	Possible PD	Possible Non-PD	
Visual Assessment Results			**Total Subjects**
POSITIVE PET Scan	158	0	158
NEGATIVE PET Scan	0	27	27

Fluorodopa F 18 is L-Dopa labeled with the short-lived radioisotope ^{18}F. The proposed package insert dose is (b) (4) 5 mCi administered intravenously. Based on literature, not their own dose finding, the applicant used a radio-dose of 4-5 mCi for the pivotal clinical trial. The total dose (primarily non-radioactive) ranged from (b) (4) to (b) (4) mg. Non-radioactive L-Dopa is currently used for the treatment of Parkinson's Disease at an oral dose that is greater than (b) (4) fold-fold higher than proposed dose.

The absorbed radiation dose for 10 human subjects (8 men and 2 women; age 50 ±8.8 yr) from intravenous administration of Fluorodopa F 18 Injection was estimated. Four men and one woman were normal volunteers and the remaining subjects had a diagnosis of typical/atypical Parkinsonian Syndromes. All subjects had normal renal function. The identified critical organ is the urinary bladder. Based upon version 3 of the MIRDOSE program, an average dose to the bladder wall in humans was estimated as 0.15 ±0.08 mGy/MBq (0.57 ±0.28 rads/mCi), the maximum bladder wall radiation dose was 0.31 mGy/MBq (1.13 rads/mCi), and the minimum was 0.07 mGy/MBq (0.27 rads/mCi). These values are below the 50-mGy (5-rad) maximum per year dose permitted by FDA for radiation workers.

Post-administration, Fluorodopa F 18 undergoes decarboxylation by the enzyme aromatic amino acid decarboxylase (AAAD) to produce Fluorodopamine F 18. In order to decrease decarboxylation by AAAD, and increase bioavailability to the brain, patients are pretreated with carbidopa, an

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inhibitor of AAAD. The applicant selected the carbidopa dose of 150 mg based on their assessment of peer-reviewed publications.

2. Question Based Review

2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

No clinical pharmacology studies were conducted by the applicant, Feinstein Institute for Medical Research (FIMR). Fourteen published literature submitted in the clinical pharmacology portion of the NDA. These studies are copied from the submission and shown in **FDA Table 1**.

FDA Table 1. Table of Clinical Pharmacology and Biopharmaceutics Studies

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5.3.1 REPORTS OF BIOPHARMACEUTIC STUDIES			
5.3.1.1 Bioavailability (BA) Study Reports			
Study #1	Cedarbaum, et. al.	Effect of Supplemental Carbidopa on Bioavailability of L-Dopa	*Clin Neuropharmacol* 1986;9:153-159
Study #2	Hoffman, et. al.	The Effects of Carbidopa Administration on 6-[^{18}F]Fluoro-L-DOPA Kinetics in Positron Emission Tomography	*J Nucl Med* 1992;33:1472-1477
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports			
5.3.1.3 In Vitro – In Vivo Correlation Study Reports			
Study #3	Cumming, et. al.	Kinetics of *In Vitro* Decarboxylation and the *In Vivo* Metabolism of 2-^{18}F- and 6-^{18}F-Fluorodopa in the Hooded Rat	*Biochem Pharmacol* 1988;37:247-250
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies			
5.3.2 REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS			
5.3.2.1 Plasma Protein Binding Study Reports			
Study #4	Cumming, et. al.	Pharmacokinetics of Plasma 6-[^{18}F]Fluoro-L-3, 4-dihydroxyphenylalanine ([^{18}F]FDOPA) in Humans	*J Cerebr Blood F Met* 1993;13:668-675
Study #5	Firnau, et. al.	Metabolites of 6-[^{18}F]Fluoro-L-Dopa in Human Blood	*J Nucl Med* 1988;29:363-369
Study #6	Kuwabara, et. al.	Regional Striatal DOPA Transport and Decarboxylase Activity in Parkinson's Disease	*J Nucl Med* 1995; 36:1226-1231
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies			
5.3.2.3 Reports of Studies Using Other Human Biomaterials			
Study #7	Snow, et. al.	Human Positron Emission Tomographic [^{18}F]Fluorodopa Studies Correlate with Dopamine Cell Counts and Levels	*Ann Neurol* 1993;34:324-330
5.3.3 REPORTS OF HUMAN PHARMACOKINETIC (PK) STUDIES			
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports			
Study #8	Huang, et. al.	Kinetics and Modeling of L-6-[^{18}F]Fluoro-DOPA in Human Positron Emission Tomographic Studies	*J Cerebr Blood F Met* 1991;11:898-913
5.3.3.2 Patient PK and Initial Tolerability Study Reports			
Study #9	Kuwabara, et. al.	Regional Striatal DOPA Transport and Decarboxylase Activity in Parkinson's Disease	*J Nucl Med* 1995; 36:1226-1231

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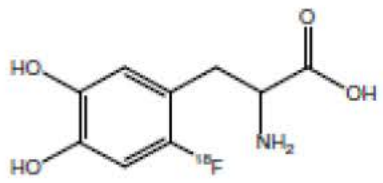
Study #10	Nagasawa, et. al.	Brain 6-[^{18}F]Fluorodopa Metabolism in Early and Late Onset of Parkinson's Disease Studied by Positron Emission Tomography	*J Neurol Sci* 1996;144:70-76
Study #11	Boyes, et. al.	Determination of Plasma [^{18}F]-6-Fluorodopa During Positron Emission Tomography: Elimination and Metabolism in Carbidopa Treated Subjects	*Life Sci* 1986;39:2243-2252
5.3.3.3 Intrinsic Factor PK Study Reports			
5.3.3.4 Extrinsic Factor PK Study Reports			
5.3.3.5 Population PK Study Reports			
5.3.4 REPORTS OF HUMAN PHARMACODYNAMIC (PD) STUDIES			
5.3.4.1 Healthy Subject PD and PK/PD Study Reports			
Study #12	Moore, et. al.	Monoamine Neuron Innervation of the Normal Human Brain: An ^{18}F-DOPA PET Study	*Brain Res* 2003;982:137-145
Study #13	Huang, et. al.	Kinetics and Modeling of L-6-[^{18}F]Fluoro-DOPA in Human Positron Emission Tomographic Studies	*J Cerebr Blood F Met* 1991;11:898-913
5.3.4.2 Patient PD and PK/PD Study Reports			
Study #14	Dietz, et. al.	Levodopa Pharmacokinetic-Pharmacodynamic Modeling and 6-[^{18}F]Levodopa Positron Emission Tomography in Patients with Parkinson's Disease	*Clin Pharmacol Ther* 2001;70:33-41

2.2. General Attributes of the Drug

2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Fluorodopa F 18 Injection is a small molecule labeled with ^{18}F, a positron emitting isotope. The active ingredient 6-[^{18}F] Fluoro-L-3, 4-dihydroxyphenylalanine has the molecular formula of $C_9H_{10}FNO_4$ and a molecular weight of 214.18 daltons. It has the following chemical structure.

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FDA Figure 1. Chemical structure of fluorodopa (6-[^{18}F] Fluoro-L-3, 4-dihydroxyphenylalanine)

Fluorodopa is formulated as an aqueous solution containing acetic acid and sodium chloride. (b) (4) The multi dose formulated drug product contains 0.0155-0.3082 GBq (0.42-8.33 mCi/mL) of fluorodopa F 18, 12.72 mg acetic acid and 108 mg sodium chloride in 12±1mL of sterile water for injection.

2.2.2. What are the proposed mechanism of action and therapeutic indications?

Fluorodopa F 18 Injection is an analogue of L-Dopa. After intravenous injection it is transported through the blood and taken up by the brain where it is decarboxylated to fluorodopamine (^{18}FDA) in dopaminergic neurons and stored in synaptic vesicles. Once released from the dopaminergic neuron, ^{18}FDA may be transported back into the pre-synaptic neuron where it may be subsequently catabolized or again stored in synaptic vesicles.

2.2.3. What are the proposed dosages and routes of administration?

The proposed dose is (b) (4) 5.0 mCi ((b) (4) 0.185GBq) administered as (b) (4).

2.2.3 What is the radiation absorbed dose associated with the proposed dose of Fluorodopa F 18 Injection?

The absorbed radiation dose for 10 human subjects (8 men and 2 women; age 50 ±8.8 yr) from intravenous administration of Fluorodopa F 18 Injection was estimated. Four men and one woman were normal volunteers and the remaining subjects had a diagnosis of typical/atypical Parkinsonian Syndromes. No known renal dysfunction conditions were noted among the subjects. The identified critical organ is the urinary bladder. Based upon version 3 of the MIRDOSE program, an average dose to the bladder wall in humans was found to be 0.15 ±0.08 mGy/MBq (0.57 ±0.28 rads/mCi) the maximum bladder wall radiation dose was 0.31 mGy/MBq (1.13 rads/mCi), and the minimum was 0.07 mGy/MBq (0.27 rads/mCi). These values are below the 50-mGy (5-rad) maximum dose permitted by FDA for radiation workers.

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2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

Currently, DaTscan (Ioflupane I 123) Injection, a radio-iodinated dopamine transporter binding ligand, has been approved for a similar indication. DaTscan is indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian Syndromes (PS).

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

No clinical pharmacology studies were performed by the applicant to support the dosing claim. The dose selected by FIMR was based on literature reports. The report that was most relied on appeared to be that of Whone, et al. (A Technique for Standardized Central Analysis of 6-Fluoro-L-Dopa PET from a Multicenter Study. Alan L. Whone, Dale L. Bailey, Philippe Remy, Nicola Pavese, and David J. Brooks. J Nucl Med, 45, 1135-1145, 2004), where 186 patients were administered a dose of 4-4.9 mCi. The dose selected by the applicant is (b) (4) than that used in the Whone et al. study.

FIMR conducted a clinical trial to support the efficacy of Fluorodopa F 18. All patients in the study were referred to FIMR by a movement disorder physician and exhibited at least two of the cardinal features of Parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). Patients entered the study with a classification of "Parkinson's Disease (PD) suspected" or "PD not suspected" from the movement disorder specialist. This clinical diagnosis by the movement disorder specialist was the standard of truth for interpretation of the PET scan results. There was 100% correlation between the visual assessment of the PET images and the clinical diagnoses. The clinical efficacy results are summarized in Table 1, below.

FDA Table 1. Clinical Efficacy Results

	Clinical Diagnosis		
	Possible PD	Possible Non-PD	
Visual Assessment Results			**Total Subjects**
POSITIVE PET Scan	158	0	158
NEGATIVE PET Scan	0	27	27

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The visual read results were supported by quantification using Striatal Occipital Ratio (SOR) values (Table 2, Table 3 and Table 4). SOR values for patients diagnosed as having Parkinsonian syndromes were lower than the SOR values of normal subjects.

FDA Table 2. Striatal Occipital Ratio (SOR) for patients with loss of dopaminergic neuron (n=158)

.

	SOR Putamen L*	SOR Putamen R	SOR Caudate L	SOR Caudate R
Range	1.5306-1.9502	1.387-1.874	1.5796-2.3661	1.7936-2.6286
Mean	1.6854	1.6698	2.0185	2.1056
Standard Deviation (SD)	0.1232	0.1964	0.1947	0.2258

*L is Left and R is Right

FDA Table 3. SOR for healthy volunteers (n=11)

	SOR Putamen L*	SOR Putamen R	SOR Caudate L	SOR Caudate R
Range	2.3415-2.6667	2.3415-2.7881	2.3763-2.8645	2.4042-2.8946
Mean	2.5452	2.5466	2.5886	2.6355
Standard Deviation (SD)	0.1297	0.1520	0.1755	0.1753

*L = Left, R = Right

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FDA Table 4. SOR values for healthy volunteers as compared to patients with negative scan

	Normal Subjects (n=11)	Patients with a Negative PET Scan (n=27)
Mean SOR (Putamen)	2.5452	2.4781
Standard Deviation	0.1297	0.1559

Subjects were followed for 3-4 years to determine the accuracy of the PET results. Follow-up confirmed the 100% accurate evaluation (applicant's analysis).

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?
2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moieties in plasma and clinically relevant tissues were not identified, only ^{18}F was monitored. No exposure-response relationship was studied.

2.4. Exposure-Response
2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?
2.4.2. What are the characteristics of the exposure-response relationships for safety?

Exposure-response, including dose-response, relationships were not studied.

Effective imaging depends on the distribution of ^{18}F. Preferential distribution to the striatum is the baseline condition that allows for effective imaging. This preferential distribution is determined by comparing the Fluorodopa uptake in the striatum to that of the occipital cortex (the occipital value is used as background). A successful scan has a sufficiently high striatal-to-occipital ratio (SOR). Within the striatum, pathology (e.g., Parkinsonian syndrome), reduces accumulation ^{18}F. A positive image, i.e, an image where a diagnosis of "Parkinsonian syndrome" is made, lacks the intensity of signal in the striatum that occurs in the absence of pathology.

2.4.3. Does this drug prolong QT/QTc Interval?

The applicant has not provided any information regarding the effect of fluorodopa to prolong QT/QTc interval. However, the mass amount of fluorodopa administered is less than (b) (4) mg. The clinical dose used to treat Parkinsons patients is 1500-1700 mg daily, or > (b) (4) X that used for imaging. We do not expect any effect of Fluorodopa F 18 on QT/QTc prolongation.

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

No exposure-response relationship was determined.

2.5. Pharmacokinetics

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2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?
2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?
2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Pharmacokinetics were not performed by the applicant. The SINEMET (carbidopa-levodopa) package insert states that the plasma half-life of levodopa is about 50 minutes, without carbidopa.

The clinical study was conducted with administration of 150 mg of carbidopa one hour prior to administration of Fluorodopa F18. The effect of carbidopa will be discussed in Section 2.7.8.

2.5.4. What are the characteristics of drug absorption?

Fluorodopa F 18 Injection is administered as a single-time intravenous injection.

2.5.5. What are the characteristics of drug distribution?

At 20 minutes post-injection, less than 50% of initial radioactivity is left in plasma. Imaging is performed one hour post-administration.

2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance study results are not reported.

2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Firnau et al (J. Nucl Med. 29, 363-369, 1988), detected four metabolites in human plasma after injection of Fluorodopa F 18: 6-[^{18}F]fluoro-O-sulfato-L-dopa, 6-[^{18}F]fluorodopamine, 3-O-methyl-6-[^{18}F]fluorodopa, and 6-[^{18}F]fluorohomovanillic acid. Estimation of the percentage of total radioactivity from each of the moieties is not reported. One of the metabolites, 3-O-methyl-6-[^{18}F]fluorodopa, appears to not accumulate in the striatal region. The contribution of the other moieties to PET imaging is unknown. Although there were quantitative differences, the metabolites identified from 6-fluoro-L-dopa in the blood were found to be the same as those identified following administration of 14-carbon-L-dopa, suggesting qualitatively similar metabolic pathway.

2.5.8. What are the characteristics of drug metabolism?

FDOPA is a substrate for AAAD and catechol-O-methyltransferase (COMT). In the striatum, FDOPA is decarboxylated to fluorodopamine by AAAD in presynaptic dopaminergic terminals. Plasma FDOPA is also converted to 3- OMFD in the periphery.

2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?

Excretion into bile or feces was not studied.

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2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is not evidence for enterohepatic recirculation for parent and/or metabolites, but only limited concentration-time data are reported, and data following non-IV administration are not reported.

2.5.11. What are the characteristics of drug excretion in urine?
Dosimetry study indicated that bladder was the target organ and that a majority of radioactivity was excreted through bladder. However, the percentages of parent and metabolites excreted in urine were not determined.

2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality results are not reported.

2.5.13. How do the PK parameters change with time following chronic dosing?

Fluorodopa F 18 Injection is administered only one time for diagnostic imaging. Repeat dosing results are not reported.

2.5.14. Is there evidence for a circadian rhythm of the PK?

There is not evidence for a circadian rhythm of the PK, but only limited concentration-time data are reported, and data are not reported by time-of-day.

2.6. Intrinsic Factors
2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

The inter-subject variability in exposure (AUC, Cmax, Cmin) is not reported.

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?
2.6.2.1. Severity of Disease State
2.6.2.2. Body Weight
2.6.2.3. Elderly

No data is reported on severity of disease state or body weight or age.

2.6.2.4. Pediatric Patients

Data from pediatric patients are not reported. A pediatric waiver has been granted to the applicant.

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2.6.2.5. Race/Ethnicity

The effect of race/ethncity on imaging or PK are not reported.

2.6.2.6. Renal Impairment

The effect of renal impairment on imaging or PK are not reported The package insert for carbidopa-levodopa does not report reanl impairment resuls, nor does it discuss dose adjustment for patients with renal impairment.

2.6.2.7. Hepatic Impairment

The effect of hepatic impairment on imaging or PK are not reported.

2.6.2.8. What pregnancy and lactation use information is available?

No pregnancy or lactation use information is available.

2.6.3. Does genetic variation impact exposure and/or response?

The effect of genetic variation impact on exposure and/or response is not reported.

2.7. Extrinsic Factors

2.7.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

I*n vitro* investigation of drug metabolism is not reported.

Inhibitors of monomaine uptake, such as anti-depressants, could potentially alter striatal accumulation of ^{18}F by inhibiting transport of any dopamine F 18 derived from fluoro dopa F 18.

2.7.2. Is the drug a substrate of CYP enzymes?

2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?

I*n vitro* investigation of drug metabolism is not reported.

2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

The ability of flurorodopa to act as an a substrate, an inhibitor and/or an inducer of transporter processes is not reported.

2.7.5. Are there other metabolic/transporter pathways that may be important?

No; the processes discussed in Section 2.5.8 are the only processes likely to be important (see also, **2.7.7.**).

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The mass dose of fluorodopa is (b) (4) mg. The clinical dose of levodopa is up to 1700 mg daily, and levodopa has not been reported to perpetrate drug interactions. Thus, the current (b) (4) mg dose of fluorodopa is unlikely to perpetrate drug interactions.

There are no reports in the imaging literature of the effect of drugs on imaging results of Fluorodopa F 18 injection.

2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors influence on exposure and/or response is not reported.

2.7.7. What are the drug-drug interactions?

The package inserts for carbidopa-levodopa products list drug interactions related to 1) an excess of monoamine effects that can occur due to excess synthesis and release of monoamines, and 2) lack of efficacy due to inhibition of D2 receptors which are the mechanism of action for L-DOPA's efficacy in Parkinsonian syndromes. Neither of these mechanisms are relevant to fluorodopa because the dose is too low to significantly alter monoamine transmission and imaging success is due to pre-synaptic accumulation, not occupation of D2 receptors. For these reasons drug interactions are unlikely.

2.7.8. Does the label specify co-administration of another drug?

The applicant administered 150 mg of carbidopa orally to all patients undergoing a Fluorodopa F 18 scan sixty minute before the injection of fluorodopa. Carbidopa is an aromatic amino acid decarbxylase (AAAD) inhibitor that does not distribute to the central nervous system. It prevents peripheral metabolism of fluorodopa, allowing increased fluorodopa to be taken up into the brain.

The following (indented) is reproduced from the SINEMET (carbidopa-levodopa) package insert

> The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours. At steady state, the bioavailability of carbidopa from SINEMET tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa.
>
> Literature estimates of the the carbidopa dose needed to maximize L-DOPA concentrations vary from 75 mg/day to 160 mg/day.

2.7.9. What other co-medications are likely to be administered to the target population?

Therapy for Parkinson's syndromes includes dopamine reuptake inhibitors and dopamine releasing agents (DRAs) such as psychostimulants (bupropion, vanoxerine etc) of the amphetamine class. It is recommended that patients not take dopamine drugs for 12 hours prior to Fluorodopa F 18 imaging.

2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

See **2.7.7.**

2.8 General Biopharmaceutics
2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?
2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?
2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?
2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?
2.8.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?
2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?
2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

Fluorodopa F 18 Injection is an intravenously administered simple saline solution; the above biopharmaceutics questions are not applicable.

2.9. Analytical Section
2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
2.9.2. Which metabolites have been selected for analysis and why?
2.9.3. For all moieties measured, is free, bound, or total measured?
2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?
2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?
2.9.5.1. What are the lower and upper limits of quantitation?
2.9.5.2. What are the accuracy, precision, and selectivity at these limits?
2.9.5.3. What is the sample stability under conditions used in the study?
2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?

The clinical pharmacology section of this application is based exclusively on literature references; FIMR performed no PK analysis. According to FIMR, there are no reviewed literature articles that discuss the bioanalytical or analytical methods included in this application. We have no details of the analytical methods used. The reviewer finds the lack of assay validation acceptable for the current NDA, as the pharmacokinetics data has limited impact on dosing and the package insert.

Reference ID: 3926908

3. Detailed Labeling Recommendations

As per discussion with medical colleagues, this NDA will not be approved. The reviewing medical division has decided to not review the package insert. We have therefore decided to not review the package insert, as any language derived might require subsequent change based upon the content of any re-submission, should such occur.

4. Appendices

4.1. Applicant's Proposed Package Insert (original, annotated)

4.2. Cover sheet and OCPB Filing/Review Form

Reference ID: 3926908

4.1. Applicant’s Proposed Package Insert (original, annotated)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CHRISTY S JOHN
06/13/2013

GENE M WILLIAMS
06/13/2013

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

/s/

CHRISTY S JOHN
04/13/2016

GENE M WILLIAMS
04/13/2016
I concur with the recommendations

NAM ATIQUR RAHMAN
04/14/2016
I agree with the recommendation of the review team.

Clinical Pharmacology Review

NDA	200-655
Submission Dates	October 22, 2012, SDN 19
Type/Category	Original-1 (Type 1- New Molecular Entity); Resubmission/After Refusal to File
Brand Name	Fluorodopa F 18 Injection
Generic Name	Fluorodopa F 18 Injection
Proposed Indication	Fluorodopa F 18 Injection is a (b) (4) used in Positron Emission Tomography (PET**)** to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations.
Dose	(b) (4) 5.0 mCi ((b) (4) 0.185GBq)
Route of Administration	Intravenous
Applicant	Feinstein Institute for Medical Research (FIMR)
Reviewing Division	Division of Clinical Pharmacology 5 (DCP 5)
Medical Division	Division of Medical Imaging Products (DMIP)
Primary Reviewer	Christy S. John, Ph.D.
Secondary Reviewer	Gene Williams, Ph.D.

Reference ID: 3324838

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Reference ID: 3324838

1. Executive Summary

The applicant, Feinstein Institute of Medical Research (FIMR), has resubmitted (after a refusal to file in March 2010) NDA (200-655) for Flurodopa F 18 Injection as a diagnostic PET (Positron Emission Tomography) imaging "to visualize dopaminergic (b) (4) in the striatum in adult patients with suspected Parkinsonian syndromes (PS). (b) (4) Fluorodopa F 18 PET is an adjunct to other diagnostic evaluations."

This application is supported by literature data along with one clinical trial conducted by the applicant. There was 100% correlation between the visual assessment of the PET images and the clinical diagnoses.

The proposed dose is an intravenous injection of (b) (4) 5 mCi. The selection of dose was based on the applicant's review of literature prior to conducting their study. The applicant used a dose of 4-5 mCi for their pivotal clinical trial. The "cold" mass dose associated with this radioactive dose is (b) (4) mg.

The primary information for clinical pharmacology review for this submission is derived from fourteen published literature submitted by the applicant. No clinical pharmacology studies were conducted by FIMR.

Fluorodopa F 18 undergoes decarboxylation by the enzyme aromatic amino acid decarboxylase (AAAD) to produce Fluorodopamine F 18. In order to decrease decarboxylation by AAAD, and increase bioavailability to the brain, patients are pretreated with carbidopa, an inhibitor of AAAD. The applicant selected the carbidopa dose of 150 mg based on their assessment of peer-reviewed publications.

No drug interaction studies have been reported in literature. However, it is not known whether drugs that are used to treat Parkinsonian syndromes can alter the disposition of Fluorodopamine F 18 or the accumulation/retention of ^{18}F in the striatum or rest of the brain. For this reason, the applicant's clinical trials required patients to discontinue any Parkinsonian medications at least 12 hours prior to the PET study. The proposed package insert includes this restriction.

No special population studies or organ impairment studies have been reported.

1.1. Recommendations

The Office of Clinical Pharmacology, Division of Clinical Pharmacology 5, has reviewed the submission NDA 203-155. The application is acceptable from a clinical pharmacology standpoint, provided an agreement is reached in labeling.

1.2. Phase 4 Requirements and Commitments

We have no recommendations for post-marketing requirements or commitments.

1.3. Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

FIMR conducted a clinical trial to support the efficacy of Fluorodopa F 18 injection for PET imaging for the determination of the loss of functional dopaminergic neurons. All patients in the study were referred to FIMR by a movement disorder physician and exhibited at least two of the cardinal features of Parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). Patients entered the study with a classification of "Parkinson's Disease (PD) suspected" or "PD not suspected" from the movement disorder specialist. This clinical diagnosis by the movement disorder specialist was the standard of truth for interpretation of the PET scan results. There was 100% correlation between the visual assessment of the PET images and the clinical diagnoses. The clinical efficacy results are summarized in Table 1.

FDA Table 1. Clinical Efficacy Results

	Clinical Diagnosis		
	Possible PD	Possible Non-PD	
Visual Assessment Results			**Total Subjects**
POSITIVE PET Scan	158	0	158
NEGATIVE PET Scan	0	27	27

Fluorodopa F 18 is L-Dopa labeled with the short-lived radioisotope ^{18}F. The proposed package insert dose is (b) (4) 5 mCi administered intravenously. Based on literature, not their own dose finding, the applicant used a radio-dose of 4-5 mCi for the pivotal clinical trial. The total dose (primarily non-radioactive) ranged from (b) (4) to (b) (4) mg. Non-radioactive L-Dopa is currently used for the treatment of Parkinson's Disease at an oral dose that is greater than (b) (4) fold-fold higher than proposed dose.

The absorbed radiation dose for 10 human subjects (8 men and 2 women; age 50 ±8.8 yr) from intravenous administration of Fluorodopa F 18 Injection was estimated. Four men and one woman were normal volunteers and the remaining subjects had a diagnosis of typical/atypical Parkinsonian Syndromes. All subjects had normal renal function. The identified critical organ is the urinary bladder. Based upon version 3 of the MIRDOSE program, an average dose to the bladder wall in humans was estimated as 0.15 ±0.08 mGy/MBq (0.57 ±0.28 rads/mCi), the maximum bladder wall radiation dose was 0.31 mGy/MBq (1.13 rads/mCi), and the minimum was 0.07 mGy/MBq (0.27 rads/mCi). These values are below the 50-mGy (5-rad) maximum per year dose permitted by FDA for radiation workers.

Post-administration, Fluorodopa F 18 undergoes decarboxylation by the enzyme aromatic amino acid decarboxylase (AAAD) to produce Fluorodopamine F 18. In order to decrease decarboxylation by AAAD, and increase bioavailability to the brain, patients are pretreated with carbidopa, an

inhibitor of AAAD. The applicant selected the carbidopa dose of 150 mg based on their assessment of peer-reviewed publications.

2. Question Based Review

2.1. What *In Vitro* and *In Vivo* Clinical Pharmacology and Biopharmaceutics studies and Clinical Studies contributed PK and/or PD information to the application?

No clinical pharmacology studies were conducted by the applicant, Feinstein Institute for Medical Research (FIMR). Fourteen published literature submitted in the clinical pharmacology portion of the NDA. These studies are copied from the submission and shown in **FDA Table 1**.

FDA Table 1. Table of Clinical Pharmacology and Biopharmaceutics Studies

5.3.1 REPORTS OF BIOPHARMACEUTIC STUDIES			
5.3.1.1 Bioavailability (BA) Study Reports			
Study #1	Cedarbaum, et. al.	Effect of Supplemental Carbidopa on Bioavailability of L-Dopa	*Clin Neuropharmacol* 1986;9:153-159
Study #2	Hoffman, et. al.	The Effects of Carbidopa Administration on 6-[^{18}F]Fluoro-L-DOPA Kinetics in Positron Emission Tomography	*J Nucl Med* 1992;33:1472-1477
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports			
5.3.1.3 In Vitro – In Vivo Correlation Study Reports			
Study #3	Cumming, et. al.	Kinetics of *In Vitro* Decarboxylation and the *In Vivo* Metabolism of 2-^{18}F- and 6-^{18}F-Fluorodopa in the Hooded Rat	*Biochem Pharmacol* 1988;37:247-250
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies			
5.3.2 REPORTS OF STUDIES PERTINENT TO PHARMACOKINETICS USING HUMAN BIOMATERIALS			
5.3.2.1 Plasma Protein Binding Study Reports			
Study #4	Cumming, et. al.	Pharmacokinetics of Plasma 6-[^{18}F]Fluoro-L-3, 4-dihydroxyphenylalanine ([^{18}F]FDOPA) in Humans	*J Cerebr Blood F Met* 1993;13:668-675
Study #5	Firnau, et. al.	Metabolites of 6-[^{18}F]Fluoro-L-Dopa in Human Blood	*J Nucl Med* 1988;29:363-369
Study #6	Kuwabara, et. al.	Regional Striatal DOPA Transport and Decarboxylase Activity in Parkinson's Disease	*J Nucl Med* 1995; 36:1226-1231
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies			
5.3.2.3 Reports of Studies Using Other Human Biomaterials			
Study #7	Snow, et. al.	Human Positron Emission Tomographic [^{18}F]Fluorodopa Studies Correlate with Dopamine Cell Counts and Levels	*Ann Neurol* 1993;34:324-330
5.3.3 REPORTS OF HUMAN PHARMACOKINETIC (PK) STUDIES			
5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports			
Study #8	Huang, et. al.	Kinetics and Modeling of L-6-[^{18}F]Fluoro-DOPA in Human Positron Emission Tomographic Studies	*J Cerebr Blood F Met* 1991;11:898-913
5.3.3.2 Patient PK and Initial Tolerability Study Reports			
Study #9	Kuwabara, et. al.	Regional Striatal DOPA Transport and Decarboxylase Activity in Parkinson's Disease	*J Nucl Med* 1995; 36:1226-1231

Reference ID: 3324838

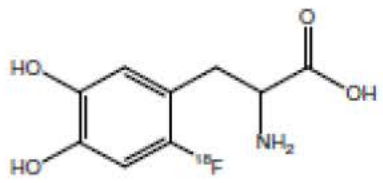
Study #10	Nagasawa, et. al.	Brain 6-[^{18}F]Fluorodopa Metabolism in Early and Late Onset of Parkinson's Disease Studied by Positron Emission Tomography	*J Neurol Sci* 1996;144:70-76
Study #11	Boyes, et. al.	Determination of Plasma [^{18}F]-6-Fluorodopa During Positron Emission Tomography: Elimination and Metabolism in Carbidopa Treated Subjects	*Life Sci* 1986;39:2243-2252
5.3.3.3 Intrinsic Factor PK Study Reports			
5.3.3.4 Extrinsic Factor PK Study Reports			
5.3.3.5 Population PK Study Reports			
5.3.4 REPORTS OF HUMAN PHARMACODYNAMIC (PD) STUDIES			
5.3.4.1 Healthy Subject PD and PK/PD Study Reports			
Study #12	Moore, et. al.	Monoamine Neuron Innervation of the Normal Human Brain: An ^{18}F-DOPA PET Study	*Brain Res* 2003;982:137-145
Study #13	Huang, et. al.	Kinetics and Modeling of L-6-[^{18}F]Fluoro-DOPA in Human Positron Emission Tomographic Studies	*J Cerebr Blood F Met* 1991;11:898-913
5.3.4.2 Patient PD and PK/PD Study Reports			
Study #14	Dietz, et. al.	Levodopa Pharmacokinetic-Pharmacodynamic Modeling and 6-[^{18}F]Levodopa Positron Emission Tomography in Patients with Parkinson's Disease	*Clin Pharmacol Ther* 2001;70:33-41

2.2. General Attributes of the Drug

2.2.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Fluorodopa F 18 Injection is a small molecule labeled with ^{18}F, a positron emitting isotope. The active ingredient 6-[^{18}F] Fluoro-L-3, 4-dihydroxyphenylalanine has the molecular formula of $C_9H_{10}FNO_4$ and a molecular weight of 214.18 daltons. It has the following chemical structure.

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FDA Figure 1. Chemical structure of fluorodopa (6-[^{18}F] Fluoro-L-3, 4-dihydroxyphenylalanine)

Fluorodopa is formulated as an aqueous solution containing acetic acid and sodium chloride. (b) (4) The multi dose formulated drug product contains 0.0155-0.3082 GBq (0.42-8.33 mCi/mL) of fluorodopa F 18, 12.72 mg acetic acid and 108 mg sodium chloride in 12±1mL of sterile water for injection.

2.2.2. What are the proposed mechanism of action and therapeutic indications?

Fluorodopa F 18 Injection is an analogue of L-Dopa. After intravenous injection it is transported through the blood and taken up by the brain where it is decarboxylated to fluorodopamine (^{18}FDA) in dopaminergic neurons and stored in synaptic vesicles. Once released from the dopaminergic neuron, ^{18}FDA may be transported back into the pre-synaptic neuron where it may be subsequently catabolized or again stored in synaptic vesicles.

2.2.3. What are the proposed dosages and routes of administration?

The proposed dose is (b) (4) 5.0 mCi ((b) (4) 0.185GBq) administered as (b) (4).

2.2.3 What is the radiation absorbed dose associated with the proposed dose of Fluorodopa F 18 Injection?

The absorbed radiation dose for 10 human subjects (8 men and 2 women; age 50 ±8.8 yr) from intravenous administration of Fluorodopa F 18 Injection was estimated. Four men and one woman were normal volunteers and the remaining subjects had a diagnosis of typical/atypical Parkinsonian Syndromes. No known renal dysfunction conditions were noted among the subjects. The identified critical organ is the urinary bladder. Based upon version 3 of the MIRDOSE program, an average dose to the bladder wall in humans was found to be 0.15 ±0.08 mGy/MBq (0.57 ±0.28 rads/mCi) the maximum bladder wall radiation dose was 0.31 mGy/MBq (1.13 rads/mCi), and the minimum was 0.07 mGy/MBq (0.27 rads/mCi). These values are below the 50-mGy (5-rad) maximum dose permitted by FDA for radiation workers.

2.2.4. What drugs (substances, products) indicated for the same indication are approved in the US?

Currently, DaTscan (Ioflupane I 123) Injection, a radio-iodinated dopamine transporter binding ligand, has been approved [redacted] (b) (4) DaTscan is indicated for striatal dopamine transporter visualization using single photon emission computed tomography (SPECT) brain imaging to assist in the evaluation of adult patients with suspected Parkinsonian Syndromes (PS).

2.3. General Clinical Pharmacology

2.3.1. What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

No clinical pharmacology studies were performed by the applicant to support the dosing claim. The dose selected by FIMR was based on literature reports. The report that was most relied on appeared to be that of Whone, et al. (A Technique for Standardized Central Analysis of 6-Fluoro-L-Dopa PET from a Multicenter Study. Alan L. Whone, Dale L. Bailey, Philippe Remy, Nicola Pavese, and David J. Brooks. J Nucl Med, 45, 1135-1145, 2004), where 186 patients were administered a dose of 4-4.9 mCi. The dose selected by the applicant is [redacted] (b) (4) than that used in the Whone et al. study.

FIMR conducted a clinical trial to support the efficacy of Fluorodopa F 18. All patients in the study were referred to FIMR by a movement disorder physician and exhibited at least two of the cardinal features of Parkinsonian syndromes (bradykinesia, rigidity, tremor, and/or gait disorder). Patients entered the study with a classification of "Parkinson's Disease (PD) suspected" or "PD not suspected" from the movement disorder specialist. This clinical diagnosis by the movement disorder specialist was the standard of truth for interpretation of the PET scan results. There was 100% correlation between the visual assessment of the PET images and the clinical diagnoses. The clinical efficacy results are summarized in Table 1, below.

FDA Table 1. Clinical Efficacy Results

	Clinical Diagnosis		
	Possible PD	Possible Non-PD	
Visual Assessment Results			**Total Subjects**
POSITIVE PET Scan	158	0	158
NEGATIVE PET Scan	0	27	27

The visual read results were supported by quantification using Striatal Occipital Ratio (SOR) values (Table 2, Table 3 and Table 4). SOR values for patients diagnosed as having Parkinsonian syndromes were lower than the SOR values of normal subjects.

FDA Table 2. Striatal Occipital Ratio (SOR) for patients with loss of dopaminergic neuron (n=158)

.

	SOR Putamen L*	SOR Putamen R	SOR Caudate L	SOR Caudate R
Range	1.5306-1.9502	1.387-1.874	1.5796-2.3661	1.7936-2.6286
Mean	1.6854	1.6698	2.0185	2.1056
Standard Deviation (SD)	0.1232	0.1964	0.1947	0.2258

*L is Left and R is Right

FDA Table 3. SOR for healthy volunteers (n=11)

	SOR Putamen L*	SOR Putamen R	SOR Caudate L	SOR Caudate R
Range	2.3415-2.6667	2.3415-2.7881	2.3763-2.8645	2.4042-2.8946
Mean	2.5452	2.5466	2.5886	2.6355
Standard Deviation (SD)	0.1297	0.1520	0.1755	0.1753

*L = Left, R = Right

FDA Table 4. SOR values for healthy volunteers as compared to patients with negative scan

	Normal Subjects (n=11)	Patients with a Negative PET Scan (n=27)
Mean SOR (Putamen)	2.5452	2.4781
Standard Deviation	0.1297	0.1559

Subjects were followed for 3-4 years to determine the accuracy of the PET results. Follow-up confirmed the 100% accurate evaluation (applicant's analysis).

2.3.2. What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?
2.3.3. Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

The active moieties in plasma and clinically relevant tissues were not identified, only ^{18}F was monitored. No exposure-response relationship was studied.

2.4. Exposure-Response
2.4.1. What are the characteristics of the exposure-response relationship for effectiveness?
2.4.2. What are the characteristics of the exposure-response relationships for safety?

Exposure-response, including dose-response, relationships were not studied.

Effective imaging depends on the distribution of ^{18}F. Preferential distribution to the striatum is the baseline condition that allows for effective imaging. This preferential distribution is determined by comparing the Fluorodopa uptake in the striatum to that of the occipital cortex (the occipital value is used as background). A successful scan has a sufficiently high striatal-to-occipital ratio (SOR). Within the striatum, pathology (e.g., Parkinsonian syndrome), reduces accumulation ^{18}F. A positive image, i.e, an image where a diagnosis of "Parkinsonian syndrome" is made, lacks the intensity of signal in the striatum that occurs in the absence of pathology.

2.4.3. Does this drug prolong QT/QTc Interval?

The applicant has not provided any information regarding the effect of fluorodopa to prolong QT/QTc interval. However, the mass amount of fluorodopa administered is less than (b) (4) mg. The clinical dose used to treat Parkinsons patients is 1500-1700 mg daily, or > (b) (4) X that used for imaging. We do not expect any effect of Fluorodopa F 18 on QT/QTc prolongation.

2.4.4. Is the dose and dosing regimen selected consistent with the known E-R relationship?

No exposure-response relationship was determined.

2.5. Pharmacokinetics

2.5.1. What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?
2.5.2. How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?
2.5.3. What are the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Pharmacokinetics were not performed by the applicant. The SINEMET (carbidopa-levodopa) package insert states that the plasma half-life of levodopa is about 50 minutes, without carbidopa.

The clinical study was conducted with administration of 150 mg of carbidopa one hour prior to administration of Fluorodopa F18. The effect of carbidopa will be discussed in Section 2.7.8.

2.5.4. What are the characteristics of drug absorption?

Fluorodopa F 18 Injection is administered as a single-time intravenous injection.

2.5.5. What are the characteristics of drug distribution?

At 20 minutes post-injection, less than 50% of initial radioactivity is left in plasma. Imaging is performed one hour post-administration.

2.5.6. Does the mass balance study suggest renal or hepatic as the major route of elimination?

Mass balance study results are not reported.

2.5.7. What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Firnau et al (J. Nucl Med. 29, 363-369, 1988), detected four metabolites in human plasma after injection of Fluorodopa F 18: 6-[^{18}F]fluoro-O-sulfato-L-dopa, 6-[^{18}F]fluorodopamine, 3-O-methyl-6-[^{18}F]fluorodopa, and 6-[^{18}F]fluorohomovanillic acid. Estimation of the percentage of total radioactivity from each of the moieties is not reported. One of the metabolites, 3-O-methyl-6-[^{18}F]fluorodopa, appears to not accumulate in the striatal region. The contribution of the other moieties to PET imaging is unknown. Although there were quantitative differences, the metabolites identified from 6-fluoro-L-dopa in the blood were found to be the same as those identified following administration of 14-carbon-L-dopa, suggesting qualitatively similar metabolic pathway.

2.5.8. What are the characteristics of drug metabolism?

FDOPA is a substrate for AAAD and catechol-O-methyltransferase (COMT). In the striatum, FDOPA is decarboxylated to fluorodopamine by AAAD in presynaptic dopaminergic terminals. Plasma FDOPA is also converted to 3- OMFD in the periphery.

2.5.9. Is there evidence for excretion of parent drug and/or metabolites into bile?

Excretion into bile or feces was not studied.

2.5.10. Is there evidence for enterohepatic recirculation for parent and/or metabolites?

There is not evidence for enterohepatic recirculation for parent and/or metabolites, but only limited concentration-time data are reported, and data following non-IV administration are not reported.

2.5.11. What are the characteristics of drug excretion in urine?
Dosimetry study indicated that bladder was the target organ and that a majority of radioactivity was excreted through bladder. However, the percentages of parent and metabolites excreted in urine were not determined.

2.5.12. Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Dose proportionality results are not reported.

2.5.13. How do the PK parameters change with time following chronic dosing?

Fluorodopa F 18 Injection is administered only one time for diagnostic imaging. Repeat dosing results are not reported.

2.5.14. Is there evidence for a circadian rhythm of the PK?

There is not evidence for a circadian rhythm of the PK, but only limited concentration-time data are reported, and data are not reported by time-of-day.

2.6. Intrinsic Factors
2.6.1. What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

The inter-subject variability in exposure (AUC, Cmax, Cmin) is not reported.

2.6.2. Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?
2.6.2.1. Severity of Disease State
2.6.2.2. Body Weight
2.6.2.3. Elderly

No data is reported on severity of disease state or body weight or age.

2.6.2.4. Pediatric Patients

Data from pediatric patients are not reported. A pediatric waiver has been granted to the applicant.

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2.6.2.5. Race/Ethnicity

The effect of race/ethncity on imaging or PK are not reported.

2.6.2.6. Renal Impairment

The effect of renal impairment on imaging or PK are not reported The package insert for carbidopa-levodopa does not report reanl impairment resuls, nor does it discuss dose adjustment for patients with renal impairment.

2.6.2.7. Hepatic Impairment

The effect of hepatic impairment on imaging or PK are not reported.

2.6.2.8. What pregnancy and lactation use information is available?

No pregnancy or lactation use information is available.

2.6.3. Does genetic variation impact exposure and/or response?

The effect of genetic variation impact on exposure and/or response is not reported.

2.7. Extrinsic Factors

2.7.1. Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

I*n vitro* investigation of drug metabolism is not reported.

Inhibitors of monomaine uptake, such as anti-depressants, could potentially alter striatal accumulation of ^{18}F by inhibiting transport of any dopamine F 18 derived from fluoro dopa F 18.

2.7.2. Is the drug a substrate of CYP enzymes?

2.7.3. Is the drug an inhibitor and/or an inducer of enzymes?

I*n vitro* investigation of drug metabolism is not reported.

2.7.4. Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

The ability of flurorodopa to act as an a substrate, an inhibitor and/or an inducer of transporter processes is not reported.

2.7.5. Are there other metabolic/transporter pathways that may be important?

No; the processes discussed in Section 2.5.8 are the only processes likely to be important (see also, **2.7.7.**).

The mass dose of fluorodopa is (b) (4) mg. The clinical dose of levodopa is up to 1700 mg daily, and levodopa has not been reported to perpetrate drug interactions. Thus, the current (b) (4) mg dose of fluorodopa is unlikely to perpetrate drug interactions.

There are no reports in the imaging literature of the effect of drugs on imaging results of Fluorodopa F 18 injection.

2.7.6. What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors influence on exposure and/or response is not reported.

2.7.7. What are the drug-drug interactions?

The package inserts for carbidopa-levodopa products list drug interactions related to 1) an excess of monoamine effects that can occur due to excess synthesis and release of monoamines, and 2) lack of efficacy due to inhibition of D2 receptors which are the mechanism of action for L-DOPA's efficacy in Parkinsonian syndromes. Neither of these mechanisms are relevant to fluorodopa because the dose is too low to significantly alter monoamine transmission and imaging success is due to pre-synaptic accumulation, not occupation of D2 receptors. For these reasons drug interactions are unlikely.

2.7.8. Does the label specify co-administration of another drug?

The applicant administered 150 mg of carbidopa orally to all patients undergoing a Fluorodopa F 18 scan sixty minute before the injection of fluorodopa. Carbidopa is an aromatic amino acid decarbxylase (AAAD) inhibitor that does not distribute to the central nervous system. It prevents peripheral metabolism of fluorodopa, allowing increased fluorodopa to be taken up into the brain.

The following (indented) is reproduced from the SINEMET (carbidopa-levodopa) package insert

> The plasma half-life of levodopa is about 50 minutes, without carbidopa. When carbidopa and levodopa are administered together, the half-life of levodopa is increased to about 1.5 hours. At steady state, the bioavailability of carbidopa from SINEMET tablets is approximately 99% relative to the concomitant administration of carbidopa and levodopa.
>
> Literature estimates of the the carbidopa dose needed to maximize L-DOPA concentrations vary from 75 mg/day to 160 mg/day.

2.7.9. What other co-medications are likely to be administered to the target population?

Therapy for Parkinson's syndromes includes dopamine reuptake inhibitors and dopamine releasing agents (DRAs) such as psychostimulants (bupropion, vanoxerine etc) of the amphetamine class. It is recommended that patients not take dopamine drugs for 12 hours prior to Fluorodopa F 18 imaging.

2.7.10. Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

See **2.7.7.**

2.8 General Biopharmaceutics

2.8.1. Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2. How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1. What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2. If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3. What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

2.8.4. Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

2.8.5. If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

Fluorodopa F 18 Injection is an intravenously administered (b) (4) solution; the above biopharmaceutics questions are not applicable.

2.9. Analytical Section

2.9.1. How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

2.9.2. Which metabolites have been selected for analysis and why?

2.9.3. For all moieties measured, is free, bound, or total measured?

2.9.4. What bioanalytical methods are used to assess concentrations of the measured moieties?

2.9.5. What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

2.9.5.1. What are the lower and upper limits of quantitation?

2.9.5.2. What are the accuracy, precision, and selectivity at these limits?

2.9.5.3. What is the sample stability under conditions used in the study?

2.9.5.4. What is the plan for the QC samples and for the reanalysis of the incurred samples?

The clinical pharmacology section of this application is based exclusively on literature references; FIMR performed no PK analysis. According to FIMR, there are no reviewed literature articles that discuss the bioanalytical or analytical methods included in this application. We have no details of the analytical methods used. The reviewer finds the lack of assay validation acceptable for the current NDA, as the pharmacokinetics data has limited impact on dosing and the package insert.

3. Detailed Labeling Recommendations

As per discussion with medical colleagues, this NDA will not be approved. The reviewing medical division has decided to not review the package insert. We have therefore decided to not review the package insert, as any language derived might require subsequent change based upon the content of any re-submission, should such occur.

4. Appendices

4.1. Applicant's Proposed Package Insert (original, annotated)

4.2. Cover sheet and OCPB Filing/Review Form

4.1. Applicant's Proposed Package Insert (original, annotated)

7 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

CHRISTY S JOHN
06/13/2013

GENE M WILLIAMS
06/13/2013