Use of exploratory IND for Early phase clinical trials using PET or SPECT imaging

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Imaging Biomarker Development and Application

**Chemistry**
- Ligand synthesis, radiolabeling

**Pre-clinical**
- In vitro assays
- In vivo non-human primate imaging - optimize outcome

**Clinical**
- POC/Dose efficacy
  - Optimize Quantitative imaging outcome
  - Identify imaging sites, establish acquisition requirements (network)
  - Test/re-test
  - Human - dosimetry
  - Define core imaging lab outcome and analysis

**Ligand optimization**
- Non-human primate
  - Target selectivity/specificity
  - Dose occupancy
  - Disease models

**Ligand Production and Distribution**
- Coordination of Phase 2-4 multi-site imaging studies using core lab to manage image acquisition, QC, analysis (CLIC)

**Production site setup**
- Innovation

**Validation**
- Application
Obstacles to Developing Imaging Biomarkers for CNS Drug Development

Most radiopharmaceuticals fail in development (inadequate brain penetrance, poor signal:noise, unstable in vivo, etc)

Expensive and time-consuming to develop - need in vitro, in vivo, and toxicology assessments

Requires validation in human studies - determine optimal quantitative measures and test/retest reproducibility

Difficult to use imaging biomarkers in multicenter trials requiring robust quantitative measures owing to technical factors related to instrumentation, acquisition protocol, radiochemistry, regulatory issues, etc.
In its March 2004 *Critical Path Report*, the FDA explained that to reduce the time and resources expended on candidate products that are unlikely to succeed, new tools are needed to distinguish earlier in the process those candidates that hold promise from those that do not.
Investigators, and Reviewers
Exploratory IND Studies

http://www.fda.gov/cder/guidance/index.htm

January 2006
Pharmacology/Toxicology
For the purposes of this guidance the phrase *exploratory IND study* is intended to describe a clinical trial that

- is conducted early in phase 1,
- involves very limited human exposure, and
- has no therapeutic or diagnostic intent (e.g., screening studies, microdose studies).
Exploratory IND Approach

Exploratory IND studies usually involve very limited human exposure and have no therapeutic or diagnostic intent. Such studies can serve a number of useful goals. For example, an exploratory IND study can help sponsors

- Determine whether a mechanism of action defined in experimental systems can also be observed in humans (e.g., a binding property or inhibition of an enzyme)

- Provide important information on pharmacokinetics (PK)

- Select the most promising lead product from a group of candidates designed to interact with a particular therapeutic target in humans, based on PK or pharmacodynamic (PD) properties

- Explore a product’s biodistribution characteristics using various imaging technologies
1. Clinical studies of pharmacokinetics or imaging

Microdose studies are designed to evaluate pharmacokinetics or imaging of specific targets and are designed not to induce pharmacologic effects. Because of this, the risk to human subjects is very limited, and information adequate to support the initiation of such limited human studies can be derived from limited nonclinical safety studies.

A microdose is defined as less than 1/100th of the dose of a test substance calculated (based on animal data) to yield a pharmacologic effect of the test substance with a maximum dose of <100 micrograms (for imaging agents, the latter criterion applies).

FDA currently accepts the use of extended single-dose toxicity studies in animals to support single-dose studies in humans.

Because micro dose studies involve only single exposures to microgram quantities of test materials and because such exposures are comparable to routine environmental exposures, routine genetic toxicology testing is not needed. For similar reasons, safety pharmacology studies are also not recommended.
Existing regulations allow a great deal of flexibility in the amount of data that needs to be submitted with any IND application, depending on the goals of an investigation, the specific human testing being proposed, and the expected risks. Sponsors have not taken full advantage of that flexibility, and limited, early phase 1 studies, such as those described in this guidance, are often supported by a more extensive preclinical database than is needed for those studies alone.

The common theme throughout this guidance is that, depending on the study, the preclinical testing programs for exploratory IND studies can be less extensive than for traditional IND studies. This is because for the approaches discussed in this guidance, which involve administering sub-pharmacologic doses of a candidate product or products, the potential risks to human subjects are less than for a traditional phase 1 study.
Application for CNS

In vitro assessments

In vitro binding – determine affinity for target and selectivity

Autoradiography and functional assays (if appropriate)
In vivo baboon/rhesus studies

- Initial injection to assess brain penetrance, washout, metabolites.
- Follow-up injections to develop quantitative outcome measures (bolus vs continuous infusion paradigm)
- Displacement studies to assess tracer specificity and selectivity
- Dose response at target
Based on NHP studies preparation of an expIND for human studies

expIND allows testing of radiotracers in humans (approx N=30)
Human Validation Studies

Human studies with an expIND

- Initial studies to assess brain penetrance, specific uptake, metabolites to establish quantitative outcome measure
- Test retest reliability
- Dose response and displacement studies with specific and selective receptor agents
- Human dosimetry
Subsequent human studies will require a full IND with a complete tox package.

For promising radiotracers, the tox package can be initiated while the human validation studies are underway.

Subsequent human studies will depend on the needs of the sponsor.
$[^{123}\text{I}] \text{MNI-420}$

Adenosine A2a
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I. Introductory Statement of Purpose and General Plan

The four main objectives of this Phase I eIND application are:

To assess the dynamic uptake and washout of $[^{123}\text{I}]$ MNI-420 in brain using single photon emission computed tomography (SPECT) in healthy subjects.

To perform blood metabolite characterization of $[^{123}\text{I}]$ MNI-420 in healthy subjects to determine the metabolic fate and nature of metabolites in assessment of $[^{123}\text{I}]$ MNI-420 as a single photon computed tomography (SPECT) brain imaging agent.

To quantify the density of A2a in Huntington Disease and Parkinson Disease.

To determine the preliminary whole body distribution and elimination following intravenous injection of $[^{123}\text{I}]$ MNI-420 in healthy subjects.
Chemistry Validation:
Successful labeling runs
Purity, Identity, Strength, Sterility, no Pyrogen at release and at end of expiration
III. Chemistry—Preparation and Controls

A-Master Production and Control Record (MPCR)

1-Descriptive name of drug:  
*Synonyms:*

2-Structure  
- Final dosage form and route of administration:  
  *Sterile, apyrogenic solution for intravenous administration*

3-List of components by name (in final vial)
4-Quantitative Composition of Drug

- Each dose contains: $[^{123}\text{I}]\text{MNI-420}$, ascorbic acid, saline
- *Calculations*: Assuming a dose of 5 mCi and specific activity of nlt 5,000 mCi/µmol, maximum amount of carrier in the dose = $(5 \text{ mCi}) / (5,000 \text{ mCi/µmol}) = 0.001 \text{ mmol}$, which corresponds to the mass amount of $(0.001 \text{ mmol}) \times (395.2 \text{ mg/µmol}) = 0.4 \text{ µg}$.

5-Theoretical yield and limits

- Theoretical yield is 100% assuming loss-free incorporation of the radiolabel into the radiolabeled compound and loss-free processing. Actual yields in radiochemical preparation of $[^{123}\text{I}]\text{MNI-420}$ can be expected to be in the range of 19–65%.

6-Description of source and preparation of new drug substance

7-Description of containers, closures, and packaging materials
8- Labels and labeling
9- Preparation and quality control instructions
   ▪ See attached batch record

10- Specifications for approval or rejection
11- Special notations and precautions

B. Preliminary Data
1- Process Validation
2- Stability Data and Expiration Dating
3- Bacterial Endotoxin (LAL) Pyrogen Test Limits
4- Solvents and metal residuals

C. Facilities for Preparation and Quality Control
1- Preparation Area
2- Approved Components Area
3- Quarantine and Rejected Components Area
D. Procedures for Quality Control

1- Radiochemical Purity
2- pH
3- Pyrogen
4- Sterility test
5- Strength
6- Visual Inspection

E. Component Specifications
Preclinical Experimentation

In vitro studies
Assays of A2a employed for the human Adenosine A2a (Cerep)

Baboon studies A series of SPECT investigations were conducted involving bolus injection of $^{[123]}$I MNI-420 in ovariectomized female baboon (*Papio anubis*). A total of 20 $^{[123]}$I MNI-420 SPECT studies were performed evaluating the regional brain uptake and washout of radioactivity and the effects of displacement with caffeine and Preladenant

Safety data
Following the induction of anesthesia through the end of the study heart rate, respiratory rate, blood pressure and temperature were monitored every fifteen minutes.

Vital sign data from each $^{[123]}$I MNI-420 injection is included in Appendix 3 of this submission. Briefly, there were no systematic effects noted on vital signs following $^{[123]}$I MNI-420 injection.

Brain uptake and washout

Image Processing

Conclusion:
Examples of MNI radiotracer development
$^{123}$I-MNI420

An Adenosine A2a tracer

Results
[\textsuperscript{123}I]MNI-420: Cynomolgus brain uptake

Total Injection: 13.6 mCi (bolus)
Brain uptake: 0.27 mCi (~2%)
[\textsuperscript{123}I]MNI-420: SPECT scan in Cynomolgus

Maximum striatum/celebellum ratio \(\sim4-5\)
A2a SPECT Radioligand $^{123}$I-MNI-420 in Non-Human Primate Studies

$^{123}$I-MNI-420 shows intense striatal uptake in baboon

Striatal $^{123}$I-MNI-420 uptake in baboon is displaced by preladenant, a specific A2a antagonist
Establish quantitative outcome
Test retest reliability
Dosimetry
Receptor Occupancy

$[^{123}\text{I}]-\text{MNI420} – \text{Human validation}$
A2a Radioligand $^{123}$I-MNI-420 and SPECT in Human Studies

Strong Enrichment in Caudate, Putamen, and Globus Pallidus with lower diffuse signal in other brain regions
## Table 1: Test/Retest variability assessment of the binding potential in the striatum derived using different methods

<table>
<thead>
<tr>
<th></th>
<th>Subject 09</th>
<th></th>
<th>Subject 10</th>
<th></th>
<th>Subject 15</th>
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<tbody>
<tr>
<td></td>
<td>Test</td>
<td>Retest</td>
<td>Variability</td>
<td>Test</td>
<td>Retest</td>
<td>Variability</td>
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<tr>
<td>BPnd from 2T</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.26</td>
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<tr>
<td>BPnd from Logan</td>
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<td>NA</td>
<td>NA</td>
<td>1.09</td>
<td>1.16</td>
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<tr>
<td>BPnd from SRTM</td>
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<td>0.77</td>
<td>4.8%</td>
<td>1.06</td>
<td>0.97</td>
<td>9.1%</td>
</tr>
<tr>
<td>BPnd from Logan non invasive</td>
<td>0.79</td>
<td>0.77</td>
<td>3.0%</td>
<td>1.05</td>
<td>0.99</td>
<td>6.4%</td>
</tr>
<tr>
<td>Ratio-1 (90 to 150min)</td>
<td>0.87</td>
<td>0.9</td>
<td>3.4%</td>
<td>1.15</td>
<td>1.09</td>
<td>5.4%</td>
</tr>
</tbody>
</table>
MNI-420
Administration of a cup of coffee
[\textsuperscript{18}F]-MNI654
[\textsuperscript{18}F]-MNI659

PDE10 tracers
Chemistry: $[^{18}\text{F}]\text{MNI654}$ and $[^{18}\text{F}]\text{MNI659}$
Non Human Primate Studies
Methods

Two non-human primate rhesus macaque

Bolus injection of 181 ± 7 MBq of [\(^{18}\)F]MNI654 or 167 ± 30 of [\(^{18}\)F]MNI659

Arterial blood for metabolite-corrected radioactivity

T1-weighted MRI, PET imaging on Siemens Focus

PET images co-registered to individual MRI
  • Time Activity Curves extracted from VOI drawn on MRI

Binding potential \( BP_{nd} \) calculated using 2T (from distribution volume \( V_T \)) or SRTM using cerebellum as reference

Occupancy of blockade studies derived from \( BP_{nd} \)
Blockade studies with MP10

MP10 administered over 30min, 35min prior to $[^{18}\text{F}]\text{MNI654}$ or $[^{18}\text{F}]\text{MNI659}$ bolus injection

Doses of 1.8, 0.6, 0.2 and 0.07 mg/kg tested

High blockade of the MNI654 or MNI659 signal by MP10 in the PDE10A rich regions
Blockade studies with MP10

$[^{18}F]$MNI654 and $[^{18}F]$MNI659 signal blocked in a dose-dependent manner by MP10

Occupancy $> 85\%$ at 1.8mg/kg

Similar occupancy using 2T (invasive) or SRTM (non-invasive)

Similar to published results with $[^{11}C]$MP10
Human Studies
Brain data acquisition: test/retest

T1-weighted MRI, PET imaging on ECAT HR+

Arterial blood for metabolites and plasma activity

$[^{18}F]MNI659$: 3D Dynamic imaging over 3.5h

- 5 healthy controls 29-47 yrs (36 ± 7): 4 males, 1 female
- Bolus injection of 177 ± 26 MBq (1.1 ± 0.9 µg)

$[^{18}F]MNI654$: 3D Dynamic imaging over 5.5h

- 2 healthy male controls, 51 and 54 yrs
- Bolus injection of 171 ± 23 MBq (0.7 ± 0.4 µg)
Brain data processing

PET images motion-corrected and realigned

PET images co-registered to individual MRI

Images normalized to the standard MNI space

Time Activity Curves extracted from VOI template

HPLC for plasma parent fraction and free fraction

\( V_T \) calculated using 2T or Logan

\( BP_{nd} \) calculated using 2T or Logan (from distribution volume) or SRTM using cerebellum as reference
Average images over first 90min of $[^{18}F]$MNI654 and $[^{18}F]$MNI659

Good brain penetrance

Regional uptake in accordance with PDE10A distribution

Highest uptake in striatum and GP
Regional Time Activity Curves

Max SUV $\approx 1.0$ for $[^{18}\text{F}]\text{MNI654}$

Max SUV $\approx 2.0$-2.5 for $[^{18}\text{F}]\text{MNI659}$

$[^{18}\text{F}]\text{MNI659}$ kinetics much faster than $[^{18}\text{F}]\text{MNI654}$
Similar metabolic profile for $^{18}$F]MNI654 and $^{18}$F]MNI659

- ~20% parent intact at 120 min post injection

Protein binding free fraction < 1%
MNI659 $BP_{nd}$ test/retest variability for different acquisition duration

Variability $< 10\%$ for both Logan and SRTM

Stable $BP_{nd}$ estimates for 90min of data
Summary

\(^{18}\text{F}\)MNI654 and \(^{18}\text{F}\)MNI659 blocked in dose-dependent manner by PDE10A selective MP10 in non-human primate studies

Good \(^{18}\text{F}\)MNI659 \(BP_{nd}\) reproducibility using both Logan and SRTM (reference = cerebellum) < 10%

90min of data is sufficient using Logan or SRTM

\(^{18}\text{F}\)MNI659 dosimetry is favorable (effective dose = 0.031 mSv/MBq)
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THANK YOU

Greetings from NEW HAVEN, Connecticut "The Elm City"