

PROTOCOL FULL TITLE: A randomised, balanced, double-blind two-way crossover design study to evaluate the effects of SRC kinase inhibitor, Saracatinib, on brain activity associated with visual processing in patients with Parkinson's disease Psychosis.

Protocol Short Title/Acronym: SRC inhibition as a potential target for Parkinson's disease psychosis- SCRIPT

Trial Identifiers

REC Number – **[Awaiting further information]**

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1. Study Synopsis

Title of clinical trial	A randomised, balanced, double-blind two-way crossover design study to evaluate the effects of SRC kinase inhibitor, Saracatinib, on brain activity associated with visual processing in patients with Parkinson's disease Psychosis.
Protocol Short Title/Acronym	SRC inhibition as a potential target for Parkinson's disease psychosis- SCRIPT
Trial Phase if not mentioned in title	
Sponsor name	King's College London (KCL)/ King's College Hospital (KCH)
Chief Investigator	Professor Mitul Mehta
REC number	
Medical condition or disease under investigation	Parkinson's disease Psychosis
Purpose of clinical trial	To test the effects of Saracatinib on brain activity associated with visual processing in Parkinson's disease psychosis.
Primary objective	To examine the effects of Saracatinib on brain activity associated with the visual recognition task in PD psychosis.
Secondary objective (s)	<p>Secondary:</p> <ul style="list-style-type: none"> • To examine the effects of Saracatinib on brain activity associated with visual processing in patients with PD psychosis. • To examine the effects of Saracatinib on brain connectivity within the default mode network in patients with PD psychosis. <p>Exploratory:</p> <ul style="list-style-type: none"> • To examine the effects of Saracatinib on brain connectivity with the inferotemporal cortex in patients with PD psychosis. • To examine the effects of Saracatinib on brain activity measured with EEG during a mismatch negativity paradigm in patients with PD psychosis. • To test a prediction error model for the effects of Saracatinib on brain activity measured with EEG during a mismatch negativity paradigm in patients with PD psychosis. • To examine the effects of Saracatinib on standard questionnaires of motor and non-motor experiences in patients with PD psychosis.

<p>Trial Design</p>	<p>A Randomised, balanced double blind two-way cross-over design.</p>
<p>Endpoints</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Difference between study drug and placebo in BOLD activity in the ventral visual stream during visual recognition vs. the control task measure using fMRI. <p>Secondary:</p> <ul style="list-style-type: none"> • Difference between study drug and placebo in BOLD activity in the occipito-temporal region during the visual processing task (Kanisza illusion). • Change in Mismatch negativity (MMN) in microvolts (mV) and connectivity with the posterior cingulate hub of the default mode network. <p>Exploratory:</p> <ul style="list-style-type: none"> • Seed-based connectivity from the Regions Of Interest (ROI) within the inferotemporal cortex. • Difference between study drug and placebo in MMN amplitude at FZ on EEG. • Test a prediction error model for the effects of Saracatinib on brain activity during a mismatch negativity paradigm on the EEG. • Difference between study drug and placebo in Factor summary score on the scales for assessment of positive symptoms in Parkinson’s disease (SAPS-PD) and the Neuropsychiatric Inventory (NPI).
<p>Sample Size</p>	<p>30 participants with PD psychosis to be enrolled for 26 completers.</p>
<p>Summary of eligibility criteria</p>	<p>To be considered eligible for this study participants must:</p> <ol style="list-style-type: none"> 1. Understand the study procedures and agree to participate by providing written informed consent. 2. Have a confirmed diagnosis of Parkinson’s disease using internationally accepted UK brain bank criteria. 3. Be male or female 4. Be right handed 5. Aged 40 years or over 6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12 lead ECG and vital signs measurements performed at screening and prior to administration of the initial dose of study drug. 7. Have a score of at least 22 in the Montreal Cognitive Assessment (MoCA). 8. Have a diagnosis of idiopathic PD 9. Have a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI [20]) 23 items A (delusions) and/or B (hallucinations).

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Study drug, dosage, and route of administration	AZD0530 (saracatinib) oral dose 100mg administered as two 50mg tablets
Active comparator product(s)	N/A
Maximum duration of treatment of a Subject	14 days (+/- 2 days)
Version and date of protocol amendments	V 2.2 23/08/18

2. Background & Rationale

2.1 Parkinson's disease psychosis and visual hallucinations

Parkinson's disease (PD) is a neurodegenerative condition which has a 1% prevalence in the over 60s and also affects young adults. As well as motor symptoms such as akinesia or rigidity, many patients also experience non-motor symptoms of which psychosis is the most common (Chang and Fox, 2016). Psychosis in Parkinson's disease has been identified as a spectrum of illusions, visual hallucinations, auditory hallucinations and delusions that occur throughout the course of the disease (Ffytche et al., 2017). Current treatments for Parkinson's disease psychosis include atypical antipsychotics such as quetiapine, clozapine and pimavanserin (a 5-HT_{2a} inverse agonist). Pimavanserin has recently been approved in the USA as a PD psychosis treatment; it has been shown to have an overall effect on reducing hallucinations as a whole, but not on visual hallucinations specifically. Functional neuroimaging evidence confirms dysfunctional ventral visual pathway activity in PD psychosis with altered metabolism, blood flow and brain activation following visual stimulation (Chang and Fox, 2016). Outside of the ventral visual pathways, two imaging studies in PD patients with visual hallucinations have shown altered connectivity within the default mode network, a brain system implicated in many neuropsychiatric conditions, pointing to more widespread abnormalities (Chang and Fox, 2016). Structural imaging studies show some atrophy within the ventral visual pathways, but also implicates brain regions outside of visual processing areas, including parietal, frontal, and cerebellar and hippocampal regions (Ffytche et al., 2017). Some authors have argued that the atrophy is independent of the hallucinations (Meppelink et al., 2011). Together, these studies fit with previously proposed models of PD psychosis that suggest that it is caused by both disrupted bottom-up processing of sensory information and dysfunctional top-down influences on perceptions.

2.2 The Serotonergic system and current treatments

Although many treatments for psychosis unrelated to Parkinson's disease are centred on dopaminergic therapies, post-mortem and *in-vivo* human studies have shown loss of striatal and extra-striatal serotonin markers in the course of PD, suggesting the involvement of the serotonergic system in PD (Politis and Niccolini, 2015). Furthermore, the serotonin system has also been implicated in PD psychosis. *In vivo*, [18F]-setoperone PET studies showed increased 5-HT_{2a} receptor binding in people with PD with visual hallucinations in the ventral visual pathway (Ballanger et al., 2010). A post-mortem study showed increased [3H]-ketanserin binding in the inferolateral temporal cortex in people with visual hallucinations compared to PD patients without visual hallucinations (Huot et al., 2010). Although pimavanserin has been shown to reduce hallucinations overall, it does not affect visual hallucinations specifically. Even though the serotonergic

dysfunction underpinning Parkinson’s disease psychosis is not fully understood, animal studies with psychedelics have pointed to the dimerisation of the 5-HT_{2A} and mGlu₂ receptors and the over recruitment of specific downstream signalling pathways. Src kinase inhibition is a potential mechanism for blocking the hallucinogenic effects of 5-HT_{2A} receptor agonism. Src kinase inhibitor, Saracatinib, has shown to reduce the intensity of the psychedelic effect induced by psilocybin (a naturally occurring psychedelic found in psilocybe mushrooms (Byock, 2018)) and attenuate social cognition and brain changes in healthy volunteers.

We will test the effects of Saracatinib on brain activity associated with visual processing using a visual processing task, known to be sensitive to 5-HT_{2a} receptor stimulation in previous studies with psilocybin (Carter et al., 2004), and a visual recognition task (Meppelink et al., 2009) with known sensitivity to PD psychosis, both scanned using the latest implementation of multi-echo blood oxygen level dependent (BOLD) functional Magnetic Resonance Imaging (fMRI). Resting state fMRI is a type of functional neuroimaging that allows the assessment of intrinsic correlations within known brain networks. Since alterations in resting state fMRI within the default mode network (a network of regions in the brain that have been demonstrated to have a role in image production (Catani et al., 2013)) have been shown in PD psychosis this will be an important tool to uncover potential ‘non-visual’ mechanisms modulated by Saracatinib.

2.3 Rationale for the study design

We aim to conduct a double-blind crossover design study, looking at the effects of Saracatinib and placebo treatment on 26 patients who have PD with psychosis. Existing data shows that 10 days of dosing with Saracatinib will achieve a steady state level that is known to be well tolerated in people with Alzheimer’s disease (Nygaard et al., 2015). Therefore, participants will be given an oral dose of 100mg of Saracatinib as two 50mg tablets to be taken once daily for 14 days. Participants will return to the clinic on day 14 for their final dose of Saracatinib, fMRI and EEG scans, cognitive assessments (described in section 6.2), physical examination and blood screen. There will be a minimum 2-week washout between treatment arms to avoid potential carry over effects. A cross-over design was chosen for this study to minimize the potential impact of inter-subject variability on the ability to detect a treatment effect of Saracatinib, as each subject serves as his/her own comparator. A placebo control is standard in the evaluation of novel therapeutics for neuropsychiatric disorders.

The aim of the current study is to use neuroimaging combined with psychopharmacology to provide evidence that a putative new treatment approach can modulate abnormal visual cortex activation in patients with PD psychosis. If positive, this proof of mechanism study would provide a strong platform to pursue symptom modification studies with Saracatinib.

Saracatinib is considered to be safe and well tolerated by healthy volunteers in doses up to and above the dose used in this study (100mg for 14 days (+/- 2 days)) this dose (100mg) is also well tolerated by patients with Alzheimer's disease (Nygaard et al., 2015). The most common side effects reported in multiple dose healthy volunteer studies in doses lower than 125mg were headache, papular rash, upper respiratory tract infection, loose stools, and myalgia.

2.3.1 Dose justification

An oral dose of 100mg of Saracatinib (two 50mg tablets) will be administered during the study period. Previous data from Nygaard et. al. in 2015 shows that doses between 50mg to 125mg are well tolerated in human participants with Alzheimer's disease. 100mg was the lowest dose that inhibited src-kinase activity in the periphery and was clearly detectable in the CSF. The study states that substantial nervous system penetration with an oral dose is achieved between 100 to 125mg, although at 125mg there were some safety and tolerability issues (Nygaard et al., 2015). Therefore, we have selected 100mg given o.d. for 14 days (with or without food) to achieve steady state plasma levels.

3. Trial Objectives and Design

3.1. Trial Objectives

Primary:

- To examine the effects of Saracatinib on brain activity associated with the visual recognition task in patients with PD psychosis.

Secondary:

- To examine the effects of Saracatinib on brain activity associated with visual processing in patients with PD psychosis.
- To examine the effects of Saracatinib on brain connectivity within the default mode network in patients with PD psychosis.

Exploratory:

- To examine the effects of Saracatinib on brain connectivity with the inferotemporal cortex in patients with PD psychosis.
- To examine the effects of Saracatinib on brain activity measured with EEG during a mismatch negativity paradigm in patients with PD psychosis.
- To test a prediction error model for the effects of Saracatinib on brain activity measured with EEG during a mismatch negativity paradigm in patients with PD psychosis.

- To examine the effects of Saracatinib on standard questionnaires of motor and non-motor experiences in patients with PD psychosis.

3.1.1 Primary endpoints

- Difference between study drug and placebo in BOLD activity in the ventral visual stream during visual recognition vs. the control task measure using fMRI.

3.1.2 Secondary endpoints

- Difference between study drug and placebo in BOLD activity in the occipito-temporal region during the visual processing task (Kanizsa illusion).
- Change in Mismatch negativity (MMN) in microvolts (mV) and connectivity with the posterior cingulate hub of the default mode network.

3.1.3 Exploratory endpoints

- Seed-based connectivity from the Regions of Interest (ROI) within the inferotemporal cortex.
- Difference between study drug and placebo in MMN amplitude at FZ on EEG.
- Test a prediction error model for the effects of Saracatinib on brain activity during a mismatch negativity paradigm on the EEG.
- Difference between study drug and placebo in Factor summary score on the scales for assessment of positive symptoms in Parkinson's disease (SAPS-PD) and the Neuropsychiatric Inventory (NPI).

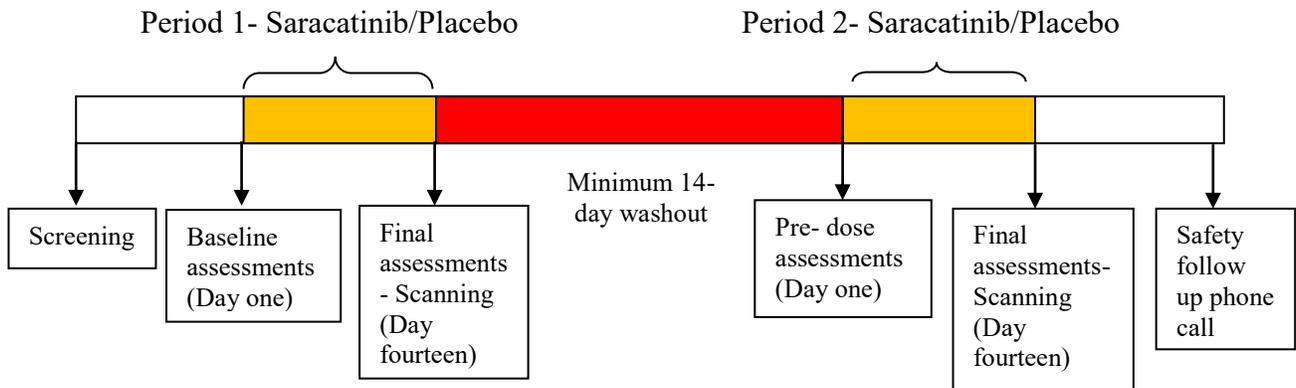
3.2 Trial Design

This will be a balanced double-blind two-way crossover design study looking at the effects of Saracatinib on brain activity associated with visual processing in patients with Parkinson's disease psychosis. This study will be carried out at a single site in the UK.

Approximately 30 patients for 26 completers with Parkinson's disease psychosis will be required to attend the study site for 5 visits; the initial screening visit, and two visits for each of two study periods. On day 1 of each study period they will attend for baseline cognitive assessments to provide a profile for the patient and will receive their first dose

of study medication (Saracatinib/placebo). They will take a dose of the medication at home every morning for the following 12 days (Days 2-13) and return to the study site on day 14 (+/- 2 days) for dosing and have their day 14 assessments performed (fMRI, EEG, Kanisza task, Meppelink task, NPI, SAPS-PD and physical examination). The two study periods will be separated by a washout period of at least 2 weeks. Approximately 14 days after their day 14 visit for study period 2 they will receive a telephone follow up call.

3.3 Trial Flowchart



Study days	Screening	Study period 1 and 2 ¹												Early termination visit ²
		Day 1- Baseline and Placebo/drug dose					Day 2-13	Day 14- Scanning and assessment day					Follow up	
		Hours						Hours						
	Pre-Dose	0	1	2	3		Pre-Dose	0	1	2	3	4		
Patient consent	X													
Physical examination	X	X						X					X	X
Neurological examination	X	X						X					X	X
Vitals ³	X	X		X	X	X		X					X	X
12- lead ECG	X	X						X						X
Oral dose of drug ⁴			X				X		X					
NPI ⁵	X	X						X						
MoCA	X	X						X						
SAPS-PD	X	X						X						
Lab safety blood and urine tests ⁶	X	X											X	
Hepatitis screen	X													
Urine drug screen	X	X						X						
Pharmacokinetic blood sample ⁷		X						X			X	X		
Non-motor symptoms ⁸		X												
SCOPA-MOTOR ⁷		X												
PD sleepiness scale ⁷		X						X						

¹ There will be a minimum 14-day washout period between study periods

² This visit will only take place if a participant decides to discontinue study treatment

³ Vitals will consist of semi recumbent blood pressure, heart rate, temperature, and respiratory rate.

⁴ 100mg of Saracatinib or placebo

⁵ To ensure that the inclusion criteria have been met. Minimum combined score of 6 in hallucinations and delusions section.

⁶ For females of child-bearing potential.

⁷ To measure the levels of Saracatinib/Placebo in the blood at baseline and scanning day.

⁸ Profiling assessments- only applicable to period one.

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Word reading (WTAR) ⁷		X														
Verbal fluency ⁸		X														
Months reversed ⁹		X														
NEVHI ⁸		X						X								
Clinical impression of severity index ⁸		X														
fMRI											X					
EEG												X				
Kanizsa illusion ¹⁰											X					
Meppelink task (visual pop-out) ⁹											X					
Visual Analogue scales								X								
PDQ		X											X			
EQ		X											X			
Dispense study medication						X										
Telephone call							X							X		X
Adverse event monitoring																



⁹ Profiling assessments- only applicable to period one

¹⁰ While in the MRI scanner.

4 Trial Medication

4.1 Study drug

Clinical study drug will be supplied by AstraZeneca.

Saracatinib will be provided as 50mg pink film coated tablets in child resistant, tamper evident high density polyethylene (HDPE) bottles for oral dosing. The bottles will contain 32 tablets in total to cover a potential 16 days of dosing.

Matching placebo tablets will also be provided.

The study drug should be stored at the temperature and in the conditions described on the drug label.

4.2 Dosing Regimen

Participants will receive a daily oral dose of Saracatinib 100mg at one study period and matched placebo at the other study period. The order in which the participant received the medication will be randomised (see section 5.5.1).

The study drug will be administered every morning for 14 days (+/- 2 days). 10 days of dosing with 100 mg Saracatinib will achieve a steady state level that is known to be well tolerated in patients with Alzheimer's disease.

An additional 2 days doses will be provided to accommodate any delays in scheduling of the Day 14 assessment visit, which may be caused by difficulty in attending the research facility, problems with the MRI scanner or other unforeseen circumstances.

There will be a minimum 14-day washout period between the final dose of period one and the first dose of period 2.

4.3 Study drug Risks

Key findings from studies conducted by AstraZeneca show that Saracatinib is a potent inhibitor of specific downstream signalling pathways via Src-kinase. It is detectable in the brain of rats and the CSF of human volunteers when administered systemically and there is minimal metabolism of Saracatinib by human hepatocytes, based on in vitro studies. However, Saracatinib is metabolised by CYP3A4 as well as being a moderate inhibitor of CYP3A4, so co-administration with moderate or potent CYP3A4 inhibitors or inducers or with medications that are metabolised by CYP3A4 (especially those with a narrow therapeutic index) should be avoided. Saracatinib has a high bioavailability and it is well-

tolerated in single and multiple doses (50, 100 or 125mg per day (Nygaard et al., 2015)) in healthy volunteers, including the 14 days of dosing we propose to use here. The compound has been administered to over 235 healthy volunteers with the most common side effects being headache (31% (Nygaard et al., 2015)), diarrhoea (31% (Nygaard et al., 2015) and 43% (Gubens et al., 2015)) and nausea (19% (Nygaard et al., 2015) and 62% (Gubens et al., 2015)). Symptoms characteristic of an influenza-like syndrome, such as fever, myalgia, pyrexia and raised C-reactive protein were evident in some volunteers receiving Saracatinib in doses of 125mg or more. More information can be found in the Investigators brochure.

Participants will be observed at all times whilst in our clinical research facility. Participants will remain at the facility until discharged home or admittance to hospital for further assessment. Throughout the study the highest standards of care for the participants will be maintained.

4.4 Drug Accountability

The investigator or designee must ensure that the study medication is used in accordance with the approved protocol and is dispensed only to participants enrolled in the study. To document appropriate use of study medication, pharmacy (on behalf of the investigator) will maintain records of all study medication delivery to the site, site inventory, use by each subject, and returns to pharmacy and destruction.

Upon receipt of study medication, pharmacy (on behalf of the investigator) will verify the contents of the shipments against the packing list. The verifier will ensure that the quantity is correct; the medication is received within the labelled storage conditions and is in good condition. If there are any discrepancies between the packing list versus the actual product received, AstraZeneca will be contacted to resolve the issue. The packing list will be filed in the pharmacy file at the investigator's site.

The investigator or his delegate must fully account for all study medication received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date is provided to the investigator.
- Verifying that the log is completed for the drug lot used to prepare each dose.
- Verifying that all study drug used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier contacting number, description of study medication,

expiry date, date and amount dispensed, and the date and amount returned to the site by the subject, including the initials of the person dispensing and receiving the study medication. The log should include all required information as a separate entry for each subject to whom study medication is dispensed.

The investigator will retain the original documentation regarding clinical study material accountability, return, and/or destruction.

The investigator will be notified of any expiry date change of clinical study material during the study conduct by AstraZeneca.

In the event of expiry date extension of supplies already at the study site, supplies may be relabelled with the new expiry date at that site. In such cases, AstraZeneca or its designee will prepare additional labels and all necessary documentation for completion of the procedure at the sites.

4.5 Storage of study drug

The study drug (Saracatinib) will be stored in the South London and Maudsley Pharmacy Department. The pharmacy will comply with all required storage conditions. If the storage conditions are not maintained, the pharmacy will quarantine the supplies and immediately report this to the CI who will confirm what action will be taken, following discussion with the supplies manufacturer.

4.6 Subject Compliance.

Participants will be telephoned on a daily basis after the initial dose visit to ensure that they are feeling well and have taken the drug. At the time of consent permission will be obtained from the participant to speak to their carer or support person, if they are not available, to ensure that the participant has taken the medication for the day.

4.7 Concomitant Medication

Participants in the study should not be on quetiapine. If patients are taking quetiapine, with permission of the treating physician and full, informed consent from the patient, they will be withdrawn from the medication for at least a month, after which they will be screened again to see if they still meet the criteria for the study. Over this month they will have regular contact with a clinician (including the drug helpline at the Maudsley Hospital) for clinical management of withdrawal symptoms and appropriate replacements will be provided depending on the symptom they are experiencing. There will be no changes to any dopaminergic medications being taken by the participant but they must be maintained on a stable dose throughout the course of the study.

Any, and all, medications or vaccines including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment or receives during the study must be recorded in the CRF along with:

Reason for use

Dates of administration including start and end dates

Dosage information including dose and frequency

4.7.1 Prohibited medication

Saracatinib is metabolised by CYP3A4 as well as being a moderate inhibitor of CYP3A4, therefore, the following medications/class of drug should not be commenced in any subject for the duration of the study:

- Moderate or potent CYP3A4 inducers or inhibitors
- Medications that are metabolised by CYP3A4 (especially those with a narrow therapeutic index)
- Quetiapine
- Anti-cholinergic medications

It is also recommended that Seville oranges, grapefruit and OTC remedies (including herbal) that interact with CYP3A4 should be avoided.

5 Selection and Withdrawal of Subjects

5.1 Inclusion Criteria

To be eligible for participation in this study, the subject must:

1. Understand the study procedures and agree to participate by providing written informed consent.
2. Have a confirmed diagnosis of Parkinson's disease using internationally accepted UK brain bank criteria.
3. Be male or female
4. Be right handed
5. Aged 40 years or over
6. Be judged to be in good health by the investigator, based on clinical evaluations including laboratory safety tests, medical history, physical examination, 12 lead ECG and vital signs measurements performed at screening and prior to administration of the initial dose of study drug.
7. Have a score of at least 22 on the Montreal Cognitive Assessment (MoCA).
8. Have a diagnosis of idiopathic PD with moderate severity

9. Have a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI [20]) 23 items A (delusions) and/or B (hallucinations).

5.2 Exclusion Criteria

The subject must be excluded from participating in the study if the subject:

1. Is a female of child bearing potential
2. Is currently taking anticholinergic medication
3. Is currently taking any medication known to be a moderate or potent CYP3A4 inducer or inhibitor.
4. Has an ongoing disability, medical or neurological history, cognitive impairment, or conditions that in the opinion of the investigator may interfere with study conduct or clinical assessments.
5. Refuses to be withdrawn from quetiapine (see section 4.7).
6. Has a family history of psychosis in a first degree relative
7. Has poor peripheral arterial/venous access or recent wrist trauma that will restrict ability to gain venous access.
8. Is currently using prescription or non-prescription drugs and herbal supplements, which are deemed to affect the integrity of the study, within 7 days or 5 half-lives (whichever is longer) prior to the first dose of trial medication. As an exception, paracetamol or acetaminophen may be used at doses of ≤ 1 g/day.
9. Has a history of sensitivity to any of the study medications or any of the excipient constituents.
10. Has a history of febrile illness within 5 days prior to the first dose
11. Has a hairstyle which would affect EEG recording.
12. Has any condition possibly affecting drug absorption (eg, gastrectomy).
13. Has a history of regular alcohol consumption exceeding 14 units/week (6 glasses of 13.0% wine (175ml), 6 pints of 4.0% lager or ale (568ml), 5 pints of 4.5% cider (568 ml) or 14 glasses of 10.0% spirits (25ml)) within 6 months of screening.
14. Uses tobacco- or nicotine-containing products in excess of the equivalent of 5 cigarettes per day.

15. Uses caffeine containing products of the equivalence of 5 cups of regular filter coffee per day
16. Has a positive urine drug screen on or after the screening visit during their active involvement in the study for opiates, methadone, cocaine, amphetamines (including MDMA), barbiturates, benzodiazepines and cannabinoids.
17. Is unwilling or unable to comply with the Lifestyle guidelines.
18. Has, in the opinion of the investigator, has any medical or psychological condition or social circumstances which would impair their ability to participate reliably in the study, or who may increase the risk to themselves or others by participating.
19. Is male and is unwilling to follow the contraception guidance or has a female partner of child bearing potential who is unwilling to follow the contraception guidance throughout the study.
20. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 x upper limit of normal (ULN)
21. Total bilirubin ≥ 1.25 x ULN
22. Known congenital long QT syndrome
23. Baseline resting QTcF > 470 ms on 12 lead ECG
24. Positive hepatitis C antibody, hepatitis B virus surface antigen or hepatitis B virus core antibody at screening
25. Known to have tested positive for human immunodeficiency virus.
26. Participation in another clinical study with an investigational product administered in the last 3 months
27. Below the lower limit of normal Hb, total WBC and neutrophils on blood counts as per the reference ranges of the laboratory conducting the tests.

5.3 Study restrictions

If considered eligible for the study subjects will:

1. Abstain from consuming alcohol from 24 hours before admission until 24 hours after discharge on day 1 and day 14 of each study period.

2. Abstain from the use of tobacco- or nicotine-containing products for 4 hours prior to admission until discharge on day 14 of each study period.
3. Abstain from unaccustomed strenuous exercise (e.g., heavy lifting, weight training, and aerobics) from 48 hours prior to day 1 until discharge on day 14 of each study period.
4. Be warned not to drive or operate machinery from the time of first dosing until 24hrs post the first dose. Taxis will be provided to transport the participants to and from the study site.

5.3.2 Reproductive restrictions

Pre-clinical in vitro studies have shown that Saracatinib is not genotoxic, however reproductive toxicity studies in rats indicate that Saracatinib can induce effects on embryofetal survival and foetal malformations. Conception must be avoided during maternal or paternal exposure to Saracatinib. Women of child bearing potential will not be included in the study. In addition, it is important that women of childbearing potential, who are the partners of male study subjects, do not become pregnant during the study and for a total period of 3 weeks after the male study subject has received his last dose of study drug (5 x elimination half-life plus 1 week).

All male subjects should avoid fathering a child by either true abstinence or use together, with their female partner/spouse, of a highly effective method of contraception (see definition below), starting from the time of study drug administration until 3 weeks after the last dose of study drug. Male subjects whose partner is pregnant should use a condom for the duration of the study and for 3 weeks afterwards.

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered highly effective birth control methods. Such methods include:

- Combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
 - Oral
 - Intravaginal
 - transdermal
- Progesterone-only hormonal contraception associated with inhibition of ovulation:
 - oral

- injectable
- implantable Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion of female partner
- Male vasectomy
- True sexual abstinence

True abstinence refers to: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Sperm Donation

Male study subjects should not donate sperm for the duration of the study and for at least 3 weeks (5 x elimination half-life plus 1 week) after the study Follow up Visit.

Pregnancy

Male subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the study subject is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow up will be completed.

Definition of women NOT of child-bearing potential

Women who are permanently or surgically sterilized or postmenopausal. Permanent sterilisation includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. Tubal occlusion is considered a highly effective method of birth control but does not absolutely exclude possibility of pregnancy. The term occlusion refers to both occluding and ligating techniques that do not physically remove the oviducts.

Definition of female post-menopausal state

Women will be considered postmenopausal if they are amenorrhoeic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women under 50 years old will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments AND with LH and FSH levels in the post-menopausal range.
- Women over 50 years of age will be considered postmenopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments.

5.4 Selection of Participants

A group of 30 patients with 26 completers with PD psychosis will be recruited from a London-wide network of patients with non-motor symptoms through recruitment infrastructure of Professor Chaudhuri which include approx. 4000 patients. Within this network are a range of patients and we will have an extended patient identification period at the beginning of the study to maximise recruitment potential from this source. Patients will also be recruited from SHAPED, an NIHR-funded programme investigating patients with visual hallucinations with Parkinson's disease, eye disease or dementia led by Dr ffytche. Finally, on-going referrals from the Movement Disorders Clinics of KHP will be assessed and screened for this study.

To be included in the study participants must have a diagnosis of PD and be deemed to have psychosis (based on NPI scores- see section 5.1) which is of moderate severity to minimize alternative diagnoses (such as Lewy Body disease).

5.5 Randomisation Procedure / Code Break

5.5.1 Randomisation

Simple crossover randomisation will be done using RNG in Matlab. The code will be done by CNS and ratified by pharmacy at King's College Hospital. The pharmacist will be unblinded and independent of the data collection team and the blinding information will not be available to the study team. Subjects will be randomised into the trial provided they have satisfied all subject selection criteria.

The plan is to recruit 30 participants with 26 completers and any dropouts will be replaced. That is the blind for 26 patients will be balanced and any replacement will have the same blinding as the dropout. Any unblinding of dropouts will be dealt with on a case-by-case basis, but typically only the medical cover will be unblinded and we have

sufficient cover to ensure they are not involved in the data collection of the replacement. The rest of the study team will always remain blinded.

5.5.2 Emergency Code Break

24hr Emergency Code Break and Medical Information will be provided by pharmacy unblinding service within pharmacy hours. A member of the clinical team will hold an envelope for out of hours. The pharmacy out of hours will be used as a back-up. Each randomised subject will be provided with a card detailing code break telephone numbers and emergency contact details. Subjects will be requested to carry this card with them at all times whilst participating in the trial.

5.6 Withdrawal of Subjects

The investigator may discontinue a subject's study participation at any time during the study, if he/she feels that the subject's continued participation is not in their best interests or if a subject deviates from the study criteria (e.g. positive DOA test) or lifestyle guidelines (e.g. reproductive restrictions, caffeine/nicotine intake). In addition, a subject may discontinue their participation without giving a reason at any time during the study.

Should a subject's participation be discontinued during a study visit after dosing, every effort should be made to perform all procedures scheduled for discharge. There is no requirement for an early termination visit in this study.

At the investigator's and sponsor's discretion, additional subjects may be added to account for discontinued or withdrawn subjects.

The investigator also has the right to withdraw patients from the study in the event of inter-current illness, AEs, SAE's, SUSAR's, protocol violations, administrative reasons, or other reasons. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient.

Participants who wish to withdraw from trial medication (IMP) will be asked to confirm whether they are still willing to provide the following.

- trial specific data at visits
- data collected as per routine clinical practice at visits

Study drug must be discontinued if:

- The participant misses two or more doses of treatment.
- The participant decides they no longer wish to continue.
- The investigator recommends it.

The reason for withdrawal will be recorded in the CRF.

5.7 Expected Duration of Trial

The end of the trial will be defined as last patient last visit; each individual subject will remain on the trial until they have completed all five visits and have had the final follow up phone call.

6 Trial Procedures and assessments

6.1 By Visit

Pre-Screening

The pre-screening procedure will involve reviewing notes and undertaking telephone interviews with the patients to evaluate whether they are suitable and interested in taking part in the study.

Screening

If the subject appears to be suitable and is interested in taking part in the study they will be provided with a patient information leaflet before they are invited to the clinic where they will have the opportunity to ask any questions or discuss the information leaflet with the Investigator or the study team. The investigator or a suitably qualified person designated by the investigator will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form, which will be stored in the Centre of neuroimaging sciences (CNS) in a locked cabinet and a copy will be provided to the patient.

Following provision of informed consent, the subject will have a medical screening, physical and psychiatric examinations including completion of the NPI, MoCA and SAPS-PD, familiarisation, and tolerability check in the mock MRI scanner (to see how well participants can tolerate the scanner environment) and basic training on the visual processing tasks. Blood and urine samples will be taken for safety tests, drug screen and pregnancy testing (if applicable).

Day 1- Baseline visit

Patients will attend the clinic on the morning of study day 1. They will be checked to make sure that they continue to meet all inclusion criteria and none of the exclusion criteria and undergo physical and neurological examinations, including completion of the NPI, MoCA, SAPS-PD, PDQ and EQ. To build the patient profile at the start of the

study, baseline questionnaire and assessments will be carried out. These include the Non-motor symptoms, SCOPA-MOTOR, PD sleepiness, WTAR, verbal fluency, months' reversed, clinical impression of severity index and the NEVHI (assessments described in section 6.2). The recall period for each of the assessments will be adapted to when the visit is taking place. Following completion of the baseline assessments the participant will receive their first dose of study medication. Saracatinib/placebo will be administered followed by a 3 hour stay during which vitals will be assessed at regular intervals. A physical examination will take place prior to discharge. On discharge, medication will be provided to be taken for the following 12 days, confirmed by daily telephone contact.

Days 2 to 13

Patients will take a dose (two 50mg tablets) of study medication at home each morning. The study team will telephone the patient/their carer each day to confirm the medication has been taken and to assess for any adverse events.

Day 14 Scanning visit

On the 14th day participants will be asked to attend the research facility in the time window of 12-16 days after their first dose, given their last dose of the study medication and then at approximately 2 hours post dose will be scanned using BOLD fMRI whilst doing the Kanizsa task and the Meppelink task. After MRI scanning is complete participants will have mismatch negativity measured using EEG. They will also have the NPI, SAPD-PD, PD sleepiness scale, NEVHI, PDQ and EQ (details of the tasks and scans outlined in section 6.2 below).

Following this, participants will undergo a physical examination and assessment by the study physician, and they will also have blood sampling for pharmacokinetic/drug exposure levels. Participants will then be discharged provided there are no concerns. There will then be a minimum 14-day washout (+/- 2 days), after which they will return for day 1 of the second study period. All study procedures (apart from the profiling assessments) on days 1 through 14 will be repeated for study period 2.

Participants will be contacted by telephone between 10 and 14 days after their final visit to check for adverse events.

Early termination visit

If a participant decides to stop the study treatment they will be given a phone call by a study physician and may be invited for an early termination visit where participants will return any unused medication undergo a physical and neurological examination, vitals, and an ECG.

6.2 Assessments

6.2.1 Profiling assessments

North-East Visual Hallucinations Interview (NEVHI)

The NEVHI is a visual complaints questionnaire that is used to assess the phenomenology of visual hallucinations (Urwylter et al., 2014). The participants will be given the NEVHI at the baseline visit to understand their hallucinations.

Wechsler Test of Adult Reading (WTAR)

The WTAR was developed to predict intellectual performance in adults and had shown to have a significant correlation with measures for intellectual functioning. It consists of 50 words with irregular 'grapheme to phoneme translation' which the participant must read out loud (Whitney et al., 2010). The WTAR takes approximately 90 seconds to complete.

Non-motor symptoms questionnaire

A nine-domain questionnaire consisting of 30 questions designed to test the frequency and severity of the non-motor symptoms of Parkinson's disease over the past month (Chaudhuri and Martinez-Martin, 2008). This questionnaire will take approximately 5 minutes to complete.

SCOPA-MOTOR scale

A 21-question test on the severity of motor symptoms PD. The test consists of three components; evaluation of motor symptoms (10 items), activities of daily living (ADL 7 items) and motor complications (4 items). All items are scored from 0 (normal) to 3 (severe) on the questionnaire (Martinez-Martin et al., 2008). This will take approximately 10 minutes to complete.

Parkinson's disease sleepiness scale

The PDSS is a 15-item scale for the assessment of sleep disorders in Parkinson's disease over the past week. The PDSS involves patients marking their response to each item on a 10cm long visual analogue scale that goes from 0 (worst) to 10 (best). All of the items of the scale are focused on nocturnal sleep except item 15 which is about daytime sleepiness. The total score on the PDSS is the sum of all of the items with a maximum score of 150 (Martinez-Martin et al., 2008).

Cognitive assessment

A brief cognitive assessment consisting of two parts; Months reversed (saying the months of the year backwards from December in 90 seconds) and Lexical fluency (giving the

patient 1 minute to name as many words as they can beginning with a particular letter) (Dubois et al., 2007).

Clinical impression of severity index

An assessment for the clinical severity of motor symptoms in 4 domains: motor signs, disability, motor complication and cognitive status. Each are is scored from 0 (normal) to 6 (very severe) and the global index from 0-24 points (Martinez-Martin et al., 2008).

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease– Rating Scale (QUIP-RS)

The QUIP-RS (Weintraub et al., 2012) is a self-report measure designed to assess the presence and the severity (on a scale from 0 to 4) of symptoms of impulse control disorders (compulsive gambling, buying, sexual behavior, and eating) and related disorders (including hobbyism, punning, and dopamine dysregulation syndrome). The questionnaire takes approximately 5 minutes to complete.

6.2.2 Study Assessments

Neuropsychiatric Inventory (NPI)

The NPI is an informant-based scale that was developed to assess neuropsychiatric symptoms. It consists of 12 items, but section A and B are delusions and hallucinations respectively. If symptoms are present, then more information is obtained through questions about frequency (scale of 1-3) and severity (scale of 1-4). The total scores are added up to get the NPI total score (Ferreira et al., 2015). An inclusion criterion for this is included in section 5.1.

Montreal Cognitive Assessment (MoCA)

The MoCA is a one-page 30-point test administered in 10 minutes. The MoCA focuses on different aspects of cognitive abilities by testing various areas such as short-term memory recall, visuospatial abilities, multiple aspects of executive functions such as attention, concentration, working memory and Language. The final questions test orientation to time and place (Nasreddine et al., 2005). Please see section 5.1 for the minimum cut off score for inclusion in this study.

Scale for the Assessment of Positive Symptoms- Parkinson's Disease (SAPS-PD)

The Scale for the Assessment of Positive Symptoms (SAPS) was originally designed for use in schizophrenia and was found to be a reliable tool for people with Parkinson's disease (Fernandez et al., 2008). Therefore, the SAPS-PD comprises of the 9 items that were found to be most frequently reported in patients with PD psychosis. It comprises of questions about hallucinations and delusions and the severity of the symptoms (Voss et al., 2013).

EEG

MMN is an ERP evoked in response to unattended changes in background stimulation. MMN is believed to reflect an automatic process of detecting a mismatch between a deviant stimulus and a sensory-memory trace. Smaller amplitudes of MMN have been consistently identified in schizophrenia subjects, showing promise as a quantitative clinical biomarker of the disease. MMN amplitude is associated with ketamine-induced psychotic experiences. MMN has demonstrated stability in clinical populations with high test-retest reliability over 1 year. Hence, MMN represents a potentially informative probe of sensory processes relevant to hallucinations/psychosis for use in experimental medicine studies of novel therapeutics. The MMN test takes approximately 10 minutes with 25 minutes set up time. Further details will be provided in the study manual.

MRI scan

The scanning protocol will comprise a localiser to ensure a good positioning in the scanner, T1-weighted structural scan (to allow registration to a template), multi-echo resting state scan (for connectivity), Kanizsa illusion, the Meppelink task and a perfusion scan using pseudo-continuous ASL (to determine changes in neurovascular coupling caused by the drug).

Kanizsa Illusion

The Kanizsa task is a task that comprises of illusory contours which are perceived edges that 'bridge gaps between aligned luminance edges' but do not exist physically. The Kanizsa task is a task that used the perceived edges to give a direct comparison of the physiological response to illusory contours which may reveal information about object perception (Mendola et al., 1999). This task will take approximately 12 minutes.

Visual pop-out task (Meppelink task)

A visual task where objects, animals and people appear out of noise and participants must press a button when they recognise what it is. A previous study by Meppelink et. Al. reported that patients with visual hallucinations and Parkinson's disease had decreased activation of the lateral occipital cortex several seconds before image recognition compared to patients with PD but no psychosis and healthy controls (Meppelink et al., 2009). This task consists of 50 images appearing from noise and each video lasts for 30 seconds. In total, the task will take approximately 20 minutes.

Visual analogue scales of physical fatigue, mental fatigue and overall health

Visual scales ranging from 0-100 where the patient marks on the scale how they would rate their physical fatigue, mental fatigue, and overall health today.

PDQ

The Parkinson’s disease questionnaire is a quality of life questionnaire specific to Parkinson’s disease (Young et al., 2013). It is composed of 39 questions and participants are asked to read a statement and indicate on a scale of ‘Never’ to ‘Always or cannot do at all’ which applies best. The questionnaire assesses difficulties of daily living across 8 dimensions. The scale can provide a single figure that can be used to assess the overall quality of life related to health.

EQ-5D

The European quality of life 5-dimension questionnaire is a standardized questionnaire for measuring health-related quality of life in 5 dimensions; mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 statements and participants are asked to tick which statement best describes their health today.

6.3 Laboratory Tests

PK and plasma exposure levels will be measured on days 1 and 14 (pre and post scanning) at approximately the same time of day to control for any bioanalytical timing effects.

Haematology

Haematology will consist of the following tests:

Erythrocytes (red blood cells)	Haemoglobin
Haematocrit	Platelets
Leukocytes (white blood cells [WBCs]) with absolute differential	

Urinalysis

Urinalysis will consist of the following tests:

Protein	Glucose
Blood	Nitrite

Urine microscopy will be performed if urinalysis is abnormal. Microscopy consists of red blood cell/high-power field, white blood cell/high-power field, and casts.

Chemistry

Chemistry evaluations will consist of the following standard chemistry panel:

Albumin	Alkaline phosphatase
ALT	AST
Blood urea nitrogen	Calcium
Carbon dioxide	Chloride
Creatinine	Glucose
Gamma-glutamyl transferase	Sodium
Potassium	Bilirubin (total), if above ULN total bilirubin will be fractionated
Protein (total)	

Diagnostic Screening

Serum

Serum diagnostic evaluations will include the following tests:

Hepatitis Screen (hepatitis A virus antibody, HBsAg, HCV antibody)
FSH, LH (females of NCBP aged under 50 only)

Urine

A urine drug screen will include the following tests:

Amphetamines	3,4-methylenedioxy-methamphetamine
Barbiturates	Methadone / Metabolite
Benzodiazepines	Opiates
Buprenorphine / Metabolite	Cocaine / Metabolites
Cannabinoids	Phencyclidine

7 Assessment of Efficacy

This study is not powered for clinical efficacy, it is powered for proof of concept and mechanism of action (change in visual cortex fMRI signal). We nonetheless record symptoms and exploratory analyses will be conducted with these. In addition, we will

explore relationships between the neuroimaging and EEG endpoints and symptoms. The symptom scores will be:

- Factor summary score on the Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD)
- Factor summary score on the Neuropsychiatric Inventory (NPI)

8 Assessment of Safety

8.1 Specification, Timing and Recording of Safety Parameters

A trained medical doctor will be available/present at all times and on all study days and be responsible for confirmation of suitability to participate, dosing, reviewing AEs, management of any side effects or medical events and discharge. At each study visit the study physician or delegate will carry out a physical exam, vital signs (blood pressure, heart rate, body temperature and respiratory rate) and ECG which will be recorded at each visit.

Participants will also be called daily to confirm they have taken the medication and for adverse event monitoring.

8.2 Procedures for Recording and Reporting Adverse Events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system and to AstraZeneca. As outlined in the exclusion criteria, females of child bearing potential will not be included in the study.

Reporting Responsibilities

King's College London and King's College Hospital have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator (and certainly no later than 24hrs) to the KHP-CTO in accordance with the current Pharmacovigilance Policy. In addition, all SAEs, SARs and SUSARs will be reported to AstraZeneca via Kinapse (astrazeneca@kinapse.com) according to the timelines outlined in Appendix A and to the research ethics committee (REC).

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The KHP-CTO will report SUSARs to the regulatory authorities (REC, competent authorities of other EEA (European Economic Area) states in which the trial is taking place.

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days to

the sponsor and reported to Kinapse as they occur and within 24 hours of knowledge. SAEs will be reported to Kinapse on a quarterly basis. Any additional relevant information must be reported within a further 8 days.

- SUSARs that are not fatal or life-threatening must be reported to Kinapse within 24 hours of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial study drug, to the REC annually.

8.2.1 Adverse events that do not require reporting

All reporting of adverse events will be as per usual standards. All adverse events will be reported, except for ongoing symptoms due to their illness. Any changes will be recorded as adverse events.

8.3 Treatment Stopping Rules

Subjects may be discontinued from the study drug in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study (i.e. data collected may still be used in data analysis).

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment. In this case, the subject will have a follow up phone call and at the discretion of a study physician, will be invited for an early termination visit.
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Safety reasons as judged by the investigator and/or sponsor and/or safety advisory committee where continued treatment may put patient at undue risk.

8.3.1 Study termination

A study advisory committee will be set-up including representatives from the study team, the clinical team, AZ and an independent chair. This committee will meet every six months to review all AE, SAE and SUSAR data as well as study progress. The committee can advise pausing or stopping the study. Any member of this committee will be able to call an ad-hoc meeting if deemed necessary based on the AE reporting for this or other studies using Saracatinib.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics

Committee will be informed within 15 days of the early termination of the trial.

9 Statistics

9.1 Sample Size

A group of approximately 30 with PD Psychosis will be enrolled in the study for 26 completers.

We used the results from (Meppelink et al., 2009), to estimate statistical power to detect the attenuation in the brain activity impairments prior to and during ‘pop-out’ recognition of degraded stimuli. This activity is reduced in those with PD psychosis with visual hallucinations compared to those without hallucinations. The signal reduction is greatest immediately before target detection or ‘pop-out’ in clusters with peaks in the occipital lobe and fusiform gyrus extending into the posterior lateral temporal lobes. The signal changes from the bilateral peaks in the fusiform gyrus were used for the power calculation. An effect size of 2/3 of that seen in Meppelink was used as a conservative estimate of the predicted change with Saracatinib (see below for justification of effect). For left fusiform prior to ‘pop-out’ the power calculation was for an effect size of 0.91 ($0.66 * 1.39$) and SD of 0.048 on the mean difference of 0.0462 requiring 15 patients with a power of 0.9 and alpha of 0.05, or 20 patients with alpha=0.01. The same calculation for the right fusiform gyrus gives a sample size of 13 patients for an effect size of 1.26 and alpha=0.01 (or a difference of 0.0595 with an SD of the difference of 0.046). Based on these calculations we propose to recruit 30 patients for at least 26 completers, with a primary endpoint of change in activity in the fusiform/posterior lateral temporal lobes. Drop-outs may be replaced at the discretion of the investigator.

For fMRI power calculations: A change in fMRI signal would indicate support for the modulation of the hypothesized mechanism. This is generally considered a valuable goal in proof of mechanism experimental studies. Understanding if the effect size of the fMRI signal change is clinically meaningful (i.e. likely to result in symptom improvement) would provide a stronger platform for translating findings for patient benefit and potentially aid outcome measure and dose selection. There are many examples of treatment studies in which fMRI changes are accompanied by symptomatic improvement. For example, in patients with psychosis (unrelated to Parkinson’s disease) and other

psychiatric disorders such as depression studies show that activation, connectivity and multivariate patterns can normalize with treatment effects [(Abbott et al., 2013), (Rubia et al., 2011)]. When studies have reported brain activation levels, existing treatments do not reverse, but instead reduce impairments. For example, responders to antidepressants show a 2/3 reduction in amygdala activation abnormality compared to no change in non-responders (Williams et al., 2015) and frontal cortex impairments reduce by a similar amount after successful antipsychotic treatment in patients with schizophrenia (Snitz et al., 2005), leading to the hypothesis that a reduction of 2/3 impairment in brain activation is a valid target for predicting symptom improvement.

9.2 Randomisation

Subjects will be randomised into the trial on a 1:1 basis provided they have satisfied all subject selection criteria. Each subject will be assigned to a treatment arm by the means of a computer-generated pseudo code.

9.3 Analysis

A statistical analysis plan (SAP) will be prepared and finalised prior to un-blinding of treatment assignments. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

We will be running a mixed effect analysis for the primary endpoints. Dropouts or missing data will not be included in the final analysis. For each analysis statistical outliers (2 SDs from mean) will be removed. Analyses with and without outliers will be provided for transparency as will a mixed effects analysis with all the data.

EEG data will be cleaned of artefacts and filtered before comparing N1 components of standard and deviant stimuli in an oddball paradigm. MRI data will go through standard pre-processing (i.e. movement correction and spatial normalisation) in SPM before fitting models of visual task events for each session (see below). These steps will occur at the single subject level and therefore will not require unblinding after this, single subject (or first level) analysis will be combined for group analysis. For the primary endpoints, the regions of interest data will be extracted and analysed using mixed effects models.

ROI Analyses

ROI endpoints will be calculated as the mean fit (beta) of the BOLD response to the task parameters within each hemisphere of the predefined brain region- inferior posterior aspect of the ventral visual system defined as a cluster peak in the fusiform gyrus extend into the lateral temporal cortex and occipital lobe. This data will be derived from

individual sessions and will be blinded to the treatment. Following unblinding, the primary comparison of interest will evaluate the effect of saracatinib in attenuating the reduced response on the visual recognition tasks, compared to placebo. The conditions to be compared are thus:

- Saracatinib vs placebo: during visual processing task
- Saracatinib vs placebo: during visual pop-out recognition

In addition, placebo scans will be compared to patients with psychosis to confirm regional brain differences.

These comparisons will be made using mixed effects models (with unstructured covariance) with fixed factors of drug (saracatinib or placebo) and session number (first or second), and a random effect of subject.

Pre-processing for ROI analysis will be identical to pre-processing for the image based analysis described below.

Image-based analyses

Image analysis will be analogous to the ROI approach, but to map at a higher spatial resolution, univariate effects. Pre-processing steps for the images will be conducted in a fixed, full-release version of SPM.

1. Slice timing correction: For each volume of the time series, a correction is performed for the differences in acquisition time between the slices with the middle slice used as reference.
2. Motion correction: For each time series, two-pass motion correction will be used. Total frame wise displacement (FD) will be calculated per volume and used to compare movement across sessions, and define movement spikes (>1mm) which will be used to derive a control regressor. If >10% of volumes are classified as spikes the particular fMRI time series will be excluded.
3. Co-registration: All the fMRI time series are co-registered using affine transformation to the same individual's T1-weighted scan.
4. Spatial normalization: All images will be registered to the standard-space (Montreal Neurological Institute) reference image. Non-linear warping will be used as per current best-practice.
5. Spatial smoothing: Data will be spatially smoothed with a Gaussian kernel (FWHM 6-8mm) to allow for gyral variability across subjects, improve the signal-to-noise ratio and ensure that the data be consistent with the assumptions of Gaussian Random Field theory used for the multiple comparisons corrections in the parametric image analysis.

Task based modelling

Onset times for events during each condition will be used to model the haemodynamic response using first level models of each session individually. For the Kanizsa task, the events are the presentation of each moving stimulus for each of the different conditions. For the visual pop-out task a finite impulse response function model will be used and will be time-locked to the detection point for the stimuli (the 'pop-out'). The time just prior to the recognition will be used for the primary end-point analysis.

EEG Data

The MMN will be analysed using the 'Neuroscan' software. Pre-processing: The slow ocular artefacts will be removed by regression with eye channels, and the data will be re-referenced to the average of the left and right Mastoids. After applying suitable filters (low pass and high pass), and rejecting any segments with gross artefact contamination, ERPs will be formed separately to the deviant/target and standard tones. The feature to be extracted for the MMN task is the magnitude in the most negative peak in the baseline corrected difference wave between the deviant and standard ERP. It is around 100 to 200ms after the deviance in the stimuli. It will be determined at FZ.

Behavioural data

Behavioural data will be summarized as means and standard deviations per subject per session and tested for normality using Shapiro-Wilk test and resulting deviations will be corrected using logarithm or square root transformations as appropriate. If reaction time data deviates from normality after transformation medians will be used for all analyses. Differences between groups will be tested with ANOVA models and drug effects with mixed effects models with fixed factors of drug (saracatinib or placebo) and session number (first or second), and a random effect of subject. We will consider use of unstructured covariance if there are sufficient degrees of freedom.

Pharmacokinetic Analyses

The plasma concentration of saracatinib will be assayed using samples taken just prior to and following the fMRI and EEG assessments and regressed against the fMRI and EEG endpoints in an exploratory analysis.

Safety Analyses

Safety parameters that will be assessed include pathology laboratory parameters, vital signs and adverse events. The parameters will be listed and summarized using standard descriptive statistics (where appropriate).

Audit trail

All recordings and processing steps will be logged and any scripts for the analyses will be saved.

10 Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc.).

11 Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to the Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study specific activity is performed. The informed consent form used in this study, and any changes made during the course of the study must be prospectively approved by the REC and HRA before use. The investigator will retain the original of each subjects' signed consent form.

12 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

Data handling, record keeping, quality control and quality assurance will adhere to the procedures to be outlined in the documentation of the Neuropharmacology Section of the Department of Neuroimaging, IoPPN, KCL. These are available on request from mitul.mehta@kcl.ac.uk.

13 Data Handling

The Chief Investigator will act as custodian for the trial data. The following guidelines will be strictly adhered to:

Patient data will be anonymised.

- All anonymised data will be stored on a password protected computer.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

14 Data Management

Electronic CRF will be used

15 Publication Policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals. Results will also be published on clinicaltrials.gov within one year of completion and in open access journals.

16 Insurance / Indemnity

[AWAITING FURTHER INFORMATION]

17 Financial Aspects

Funding to conduct the trial is provided by MRC

18 Signatures

Chief Investigator
Print name

Date

Statistician (if applicable)
Print name

Date

19 References

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Appendix A

Safety Reporting Responsibilities

Sponsor:

Trial:

AstraZeneca Reference number:

Date:

Sponsors and AstraZeneca will exchange safety information in accordance with the requirements set out in the summary table at the end of this document.

The following information is required.

Before the trial starts:

Sponsor will provide AstraZeneca with:

- A copy of the format of the SAE report form including the AZ Reference number.
- An example of the format by which SAEs (including SUSARS) will be reported from sponsor to AZ. This should include the format of any individual reports (*this may be the same form used for reporting SAEs above*) and/or the format of quarterly listings if appropriate.
- The format by which site and patient ID will be presented in safety reports so that they can be entered in a consistent way on the AZ safety database.

AstraZeneca will provide the sponsor with:

- The current IB
*An adverse event should only be considered expected for an AstraZeneca Investigational Medicinal Product (IMP) if it is included in Section 5.4 of the IB.
These will be available to access through ES²ROS – Externally Sponsored Scientific Research Operations System*
- The contact information for our safety reporting: astrazeneca@kinapse.com. All information that needs to be shared with AstraZeneca should be sent to Kinapse at the email address provided according to the guidelines set out in subsequent sections of this document.

During the Trial

Sponsor will:

- Report unblinded Suspected Unexpected Serious Adverse Reactions (SUSARs) to AstraZeneca (via Kinapse) as individual case reports as they occur
- Report blinded listings of Serious Adverse Events (SAEs) and Suspected Serious Adverse Reactions (SSAR's) to AstraZeneca on a quarterly basis.
- Inform AstraZeneca within 24 hours of knowledge of the event of any emerging safety data or actions that the Sponsor is considering as a result of a safety signal with the IMP. This includes but is not limited to:
 - Urgent safety measures to be implemented in the study
 - Safety amendments to protocol/patient information & informed consent
 - Open reports from Independent Data Monitoring Committees (IDMCs) excluding confidential reports to IDMC and minutes of IDMC meetings
 - Interactions with Regulatory Authorities (RA's)/ Ethics Committees (EC's)
 - Inform AZ on an ongoing basis of any new safety trends or signals observed during routine safety surveillance activities
- Include the following essential information in SUSAR, SSAR and SAE reports provided to AstraZeneca (initial and follow-up) :
 - AstraZeneca Reference number
 - Sponsor trial number
 - Centre number
 - Patient trial number
 - Year of birth or age
 - Sex
 - IMP(s) dose, start & stop date
 - SAE onset & stop date
 - Event term as reported by the investigator (and/or the CTCAE V4 term and grade)
 - Investigator's assessment of seriousness (ICH definitions)
 - Investigator's assessment of causality
 - SAE Outcome

During the Trial

AstraZeneca will:

- Immediately inform the sponsor of any emerging safety data or actions that AstraZeneca is considering as a result of a safety signal with the IMP. This includes but is not limited to:
 - New safety information which may alter the benefit risk assessment
 - Urgent safety measures to be implemented
- Request follow-up information on an SAE that is of interest and is related to the IMP(s).
- Provide the Sponsor with IB updates on an annual basis or as new safety information

emerges.

- Consult with the sponsor in the unlikely circumstance that code break information is required for an individual patient, should AstraZeneca need to expedite an SAE that has not been reported to RAs by the sponsor.
- Provide SAE Line Listings of the IMP if required

At the end of the Trial

Sponsor will:

- Provide safety listings (details are included in the summary table below)

Summary of Minimum Requirements for Exchange of Safety Data

Sponsors will submit safety information in compliance with clinical trial regulations and the Standard Operating Procedures of their organisation including to:

- Regulatory authorities
- Ethics committees
- Site investigators

In addition, **Sponsors will submit the following safety information to AstraZeneca:**

Category of Adverse Event/ Report	Report Type	When to send report to AZ	Method of Submission	Additional Information
SUSARs	Individual unblinded case reports (Initial and follow-up reports)	Within one (1) business day of the reports being sent to the Regulatory Authority	Email to: astrazeneca@kinapse.com	<p>Sponsor responsible for:</p> <ul style="list-style-type: none"> • Expedited reporting of all SUSARs to the RA of participating countries in line with local requirements. • Compliance with local regulations of participating countries for reporting of SUSARs to investigational sites and EC's. <p>AstraZeneca responsible for:</p> <ul style="list-style-type: none"> • Reporting SUSARs to RA's where AstraZeneca sponsored studies are being conducted with the IMP as appropriate. • Reporting SUSARs to investigators participating in any AstraZeneca sponsored studies with the IMP as required by RA's.
SAEs/ SSARs	Summary Line Listings	On a quarterly basis from the date of the first patient consent		<ul style="list-style-type: none"> • SAEs and SSARs should be provided as blinded line listings. • Where possible the listing should include only events that are new or updated since the last report.

Category of Adverse Event/ Report	Report Type	When to send report to AZ	Method of Submission	Additional Information
Annual DSUR – (EU only)	Periodic safety reports (produced for external purposes e.g. EC or RA of participating countries)	Only required if the DSUR is inconsistent with the IB.	Contact your AZ operational representative	<ul style="list-style-type: none"> Ideally any findings in the DSUR that are inconsistent with the IB should be communicated to AZ during DSUR production but at the latest in parallel to the DSUR being sent to the RA/Ethics committee. If this situation arises contact your AZ operational representative. The production of any DSUR with no new safety concerns should be confirmed in writing to your AZ operational representative.
End of Study SAEs, SSARs & SUSARs (for entry onto AZ Patient Safety database)	A cumulative final listing of all unblinded SAEs, SSAR's & SUSARs	At 'clean file' (<i>when all study queries have been answered and the database is locked</i>) at the following time points: 1. At primary analysis 2. After last patient has completed study treatment	Email to: astrazeneca@kinapse.com and to AZ operational representative	<ul style="list-style-type: none"> For blinded studies AZ require an unblinded listing of SAEs and SSARs to enable unblinding of these events on the AZ safety database. For convenience and completeness SUSARs should also be included and easily identifiable.

AstraZeneca will submit the following safety information to trial Sponsors:

Category of Adverse Event/ Report	Report Type	Frequency/ Timeframe	Method of Submission	Additional Information
SUSARs	Final CIOMS report of case (password protected)	Within 15 days of initial receipt	Email to Sponsor contact.	<ul style="list-style-type: none"> These may be provided whilst clinical studies (AZ-sponsored or externally-sponsored) are on-going or until the IMP becomes marketed. AstraZeneca will provide these over the time period stated in the bullet point above to investigators, EC's and relevant RAs involved in AstraZeneca sponsored studies.

PROTOCOL SCRIPT

				<ul style="list-style-type: none">• Sponsor will distribute these to investigators and ECs in line with local requirements.
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Contact Details

AstraZeneca:

Emerging safety data or actions:

Email to: astrazeneca@kinapse.com

General enquiries to AZ:

AZ Operational or Scientific Representative

The AstraZeneca Reference number and IMP name(s) should be included in email headers and emails should be sent in an encrypted file e.g. WinZip

Sponsor responsibility:

Periodic line listings notification:

Name of Trial Coordinator of Study:

Address:

SAE follow-up queries:

Name:

Email:

Telephone:

Unblinded Request:

Name:

Email:

Telephone:

Only organisational emails may be used