

# A clinical trial to explore the potential of ondansetron for treating hallucinations in people with Parkinson's disease

<b>Submission date</b> 10/10/2019	<b>Recruitment status</b> Stopped	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
<b>Registration date</b> 05/02/2020	<b>Overall study status</b> Stopped	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
<b>Last Edited</b> 10/04/2024	<b>Condition category</b> Nervous System Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> Record updated in last year

## Plain English summary of protocol

### Background and study aims

Visual hallucinations (seeing things that do not exist) occur in 75% of people with Parkinson's across the illness course, are often highly distressing, have a significant impact on quality of life, and are associated with dementia and earlier care home placement. NHS treatment options are currently limited to medications known as antipsychotics that are associated with significant side-effects, including sedation, falls, worsening of Parkinson's symptoms (tremor, movement co-ordination) and memory problems. Usual treatment involves quetiapine, as it is safer than other antipsychotic drugs, but of questionable effectiveness, or clozapine, which is effective but not feasible for use outside specialist units due to safety monitoring requirements. Pimavanserin, is a newly developed drug that has shown modest treatment effects, but is highly expensive, and not licensed for use in the UK. Finding treatments that are safe, effective, cost effective and practical for use in NHS clinics is a priority. Ondansetron, a drug used to treat post-operative nausea and vomiting, was identified as a highly promising candidate treatment for Parkinson's hallucinations in the early 1990s, when 16 people with Parkinson's and persistent severe visual hallucinations improved with ondansetron (12-24mg daily), 14 with complete resolution of symptoms, with no worsening of Parkinson's symptoms, memory or functional ability. Further studies were not carried out at the time because the drug was then extremely expensive. Costs are now much less (equivalent to usual treatment) and a larger trial in people with Parkinson's is feasible, timely and highly necessary

### Who can participate?

People with Parkinson's, aged over 55 years, who are experiencing hallucinations at least weekly, at a point when other approaches to treatment (altering lighting, reducing Parkinson's medication) have failed

### What does the study involve?

Those taking part will be allocated (randomly via a computerized system) to receive drug or placebo and neither the prescribing clinicians or participants will know which treatment they are taking. The dose of the study drug will increase from one (8mg or placebo) tablet, to a maximum of 3 tablets over the first 6 weeks, guided by telephone monitoring of side effects and safety (2

and 4 weeks). Treatment will then continue for a further 6 weeks. Usual treatment (quetiapine) will be available to all participants if required, to ensure that distressing symptoms are not left untreated. Face to face assessments and blood sampling will be carried out after 6 and 12 weeks treatment, and over the telephone after treatment has completed (16 and 24 weeks).

Recruitment will take place over 2 years in 15-20 NHS clinics, supported by local Research Networks and Parkinson's UK. It will also be possible for participants to refer themselves to the study. Agreed recruitment targets are 5 participants per site in the first year, and progress will be assessed 9 months into recruitment by the Trial Management Group, to identify barriers to recruitment or retention to the study and ensure that they are addressed in a timely way. There will be focus group representation on biannual trial committees that will monitor progress towards recruitment targets, safety and data management throughout the study

What are the possible benefits and risks of participating?

Ondansetron is licensed for short term use as an anti-emetic and has undergone extensive safety testing for this indication. Any observed treatment benefits are likely to outweigh the risks. There is no guarantee of any direct benefit to you as a result of participating in this research study but ondansetron may help to treat visual hallucinations and may help reduce delusions associated with Parkinson's disease. Your participation may provide information useful to the understanding of ondansetron and Parkinson's disease. Constipation, which is common in people with Parkinson's, is a known side effect of ondansetron and a dose titration phase will be used to reduce the burden of possible side effects

Where is the study run from?

University College London, UK

When is the study starting and how long is it expected to run for?

April 2020 to July 2026

Who is funding the study?

Parkinson's UK

Who is the main contact?

Dr Olga Zubko

[o.zubko@ucl.ac.uk](mailto:o.zubko@ucl.ac.uk)

## Contact information

### Type(s)

Public

### Contact name

Dr Olga Zubko

### Contact details

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+44 (0)20 3545 9073  
o.zubko@ucl.ac.uk

## Additional identifiers

**EudraCT/CTIS number**  
2019-003962-41

**IRAS number**  
266504

**ClinicalTrials.gov number**  
NCT04167813

**Secondary identifying numbers**  
17/0909, IRAS 266504

## Study information

**Scientific Title**  
Trial of Ondansetron as a Parkinson's HALLucinations Treatment

**Acronym**  
TOP HAT

**Study objectives**  
The study will test the hypothesis that flexibly dosed ondansetron (8-24mg/day) will have a clinically meaningful treatment effect on visual hallucinations in people with Parkinson's, without worsening motor or cognitive symptoms.

**Ethics approval required**  
Old ethics approval format

**Ethics approval(s)**  
Approved 03/02/2020, East of England - Cambridge East Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 2071048265; cambridgeeast.rec@hra.nhs.uk), ref: 19/EE/0377

**Study design**  
Double-blind individually randomized placebo-controlled parallel-group flexible-dose trial

**Primary study design**  
Interventional

**Secondary study design**  
Randomised parallel trial

**Study setting(s)**  
Hospital

**Study type(s)**

Treatment

**Participant information sheet**

Not available in web format, please use contact details to request a participant information sheet

**Health condition(s) or problem(s) studied**

Parkinson's hallucinations

**Interventions**

The intervention will consist of flexible dosing of ondansetron/placebo (8-24mg/day) as a treatment for Parkinson's hallucinations, with a 12-week primary outcome and follow-up to 24 weeks. The treatment dose will increase from a single daily 8 mg tablet (AM) (weeks 1 and 2), to 16 mg/day (8 mg twice daily) (weeks 3 and 4), with a further increase to 24 mg/day (8 mg AM, 16 mg PM) (weeks 5 and 6).

The study will recruit people with Parkinson's, aged over 55 years, who are experiencing hallucinations at least weekly, at a point when other approaches to treatment (altering lighting, reducing Parkinson's medication) have failed. Those taking part will be allocated (randomly via a computerized system) to receive drug or placebo and neither the prescribing clinicians or participants will know which treatment they are taking. The dose of the study drug will increase from one (8 mg or placebo) tablet, to a maximum of 3 tablets over the first 6 weeks, guided by telephone monitoring of side effects and safety (2 and 4 weeks). Treatment will then continue for a further 6 weeks. Usual treatment (quetiapine) will be available to all participants if required, to ensure that distressing symptoms are not left untreated. Face to face assessments and blood sampling will be carried out after 6 and 12 weeks treatment, and over the telephone after treatment has completed (16 and 24 weeks). Recruitment will take place over 2 years in 15-20 NHS clinics, supported by local Research Networks and Parkinson's UK. It will also be possible for participants to refer themselves to the study. Agreed recruitment targets are 5 participants per site in the first year, and progress will be assessed 9 months into recruitment by the Trial Management Group, to identify barriers to recruitment or retention to the study and ensure that they are addressed in a timely way. There will be focus group representation on biannual trial committees that will monitor progress towards recruitment targets, safety and data management throughout the study.

**Intervention Type**

Drug

**Phase**

Phase II

**Drug/device/biological/vaccine name(s)**

Ondansetron

**Primary outcome measure**

Visual Hallucinations measured using SAPS-H (12 weeks)

**Secondary outcome measures**

1. Visual hallucinations measured using SAPS-H (2, 4, 6, 12, 18, 24 weeks)
2. Delusions measured using SAPS-D (2, 4, 6, 12, 18, 24 weeks)
3. Global Severity (Impact) of symptoms measured using CGI-S (2, 4, 6, 12, 18, 24 weeks)
4. Hallucinations measured using UM-PDHQ (12 weeks)
5. Non-motor symptoms measured using NMSS (6, 12, 18, 24 weeks)
6. Proportion receiving quetiapine rescue medication at end of treatment (12 weeks) and follow-up (24 weeks) periods
7. Health-related quality of life measured using Euro-QoL, EQ-5D (6, 12, 18, 24 weeks) Parkinson's symptoms (tremor, rigidity) UPDRS III (6, 12 weeks)
8. Cognition measured using sMMSE (12 weeks)
9. ECG changes measured using QTc interval (6 weeks)
10. Tolerability measured using adverse event checklist (2, 4, 6, 12, 18, 24 weeks)
11. Pharmacokinetics measured using Venous blood drug concentration (6, 12 weeks)
12. Visual information processing measured using HVOT (12 weeks)

**Overall study start date**

14/06/2019

**Completion date**

31/07/2026

**Reason abandoned (if study stopped)**

Objectives no longer viable

## Eligibility

**Key inclusion criteria**

1. Aged over 55 years
2. Meet Brain Bank criteria for Parkinson's disease
3. Visual hallucinations have been present at least weekly in the month before screening and are moderately severe
4. On a stable dose of anti-Parkinson's medication, cholinesterase inhibitor or memantine for at least 28 days
5. Capacity to give informed consent or (if lacking) caregiver or other legal representative able to give consent
6. Pre-menopausal women, and men whose partners are of child bearing potential who agree to use effective contraception during the trial treatment period

**Participant type(s)**

Patient

**Age group**

Adult

**Lower age limit**

55 Years

**Sex**

Both

**Target number of participants**

216

**Total final enrolment**

168

**Key exclusion criteria**

1. Bradycardia (<50 bpm) (rescreen if reversible)
2. Congenital long QTc syndrome or presence of clinically significant prolongation of QTc (>460 ms for men or >470 ms for women) on ECG screening.
3. Severe hepatic failure (bilirubin >50 micromole/L)
4. Prescribed any antipsychotic medication in the past 2 weeks
5. Prescribed apomorphine
6. Prescribed tropisetron, granisetron, dolasetron
7. History of hypersensitivity to ondansetron and its excipients (or those of placebo) or drugs listed in 6
8. Participation in another Clinical Trial of an Investigational Medicinal Product (IMP) in the previous 28 days

**Date of first enrolment**

01/04/2020

**Date of final enrolment**

31/01/2025

**Locations****Countries of recruitment**

England

United Kingdom

Wales

**Study participating centre**

**Leonard Wolfson Experimental Neurology Centre**

Gower St

Bloomsbury

Epsom

United Kingdom

WC1N 3BG

**Study participating centre**

**Salford Royal NHS Foundation Trust**

Stott Lane

Manchester  
United Kingdom  
M6 8HD

**Study participating centre**  
**Pennine Acute Hospitals NHS Trust**  
Fairfield General Hospital  
Rochdale Old Road  
Bury  
United Kingdom  
BL9 7TD

**Study participating centre**  
**Cambridge University Hospitals NHS Foundation Trust**  
Hills Road  
Cambridge  
United Kingdom  
CBQ 0QQ

**Study participating centre**  
**Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust**  
Castle Ln E  
Bournemouth  
United Kingdom  
BH7 7DW

**Study participating centre**  
**Northumbria Healthcare NHS Foundation Trust**  
Unit 7-8 Silver Fox Way Cobalt Business Park  
Newcastle upon Tyne  
United Kingdom  
NE12 8EW

**Study participating centre**  
**Royal Devon and Exeter NHS Trust**  
Barrack Rd  
Exeter  
United Kingdom  
EX2 5DW

**Study participating centre**  
**Royal United Hospitals Bath**  
Combe Park  
Bath  
United Kingdom  
BA1 3NG

**Study participating centre**  
**Wrexham Maelor Hospital**  
Croesnewydd Road  
Wrexham  
United Kingdom  
LL137TD

**Study participating centre**  
**Ysbyty Gwynedd**  
Bangor  
United Kingdom  
LL57 2PW

**Study participating centre**  
**Llandudno Hospital**  
Hospital Rd  
Llandudno  
United Kingdom  
LL30 1LB

**Study participating centre**  
**Holyhead Hospital**  
Penrhos Beach Rd  
Anglesey  
Holyhead  
United Kingdom  
LL65 2QA

## **Sponsor information**

**Organisation**  
PRIMENT CTU



**Sponsor details**

UCL Medical School  
Upper 3rd Floor  
Royal Free Campus  
Rowland Hill Street  
London  
England  
United Kingdom  
NW3 2PF  
+44 (0)20 7794 0500 ext 36724  
priment@ucl.ac.uk

**Sponsor type**

University/education

**Website**

<https://www.ucl.ac.uk/priment/>

## **Funder(s)**

**Funder type**

Charity

**Funder Name**

Parkinson's UK

**Alternative Name(s)****Funding Body Type**

Private sector organisation

**Funding Body Subtype**

Associations and societies (private and public)

**Location**

United Kingdom

## **Results and Publications**

**Publication and dissemination plan**

Progress of the study will be shared with people with Parkinson's through newsletters, individual letters, and quarterly updates that will be available on Parkinson's UK and linked websites. Information will also be shared locally by Parkinson's UK and by clinicians who are leading recruitment across the UK. The research findings will be submitted for publication to high quality peer reviewed journals and shared at national and international conferences. There

will also be talks, training and seminars delivered via existing platforms for NHS service improvement and education. This includes the Parkinson's Excellence Network, which is supported by Parkinson's UK, and educational meetings led by the British Geriatric Society and the Association of British Neurologists.

### **Intention to publish date**

31/07/2027

### **Individual participant data (IPD) sharing plan**

The current data sharing plans for this study are unknown and will be available at a later date

### **IPD sharing plan summary**

Data sharing statement to be made available at a later date

### **Study outputs**

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
<a href="#">HRA research summary</a>			28/06/2023	No	No