Clinical trial results:
A placebo controlled double blind randomised controlled proof of concept study of zolpidem for the treatment of motor and cognitive deficits in late-stage Parkinson's

Summary

EudraCT number	2017-004297-34
Trial protocol	GB
Global end of trial date	31 October 2019

Results information

Result version number	v1 (current)
This version publication date	26 September 2020
First version publication date	26 September 2020

Trial information

Trial identification

Sponsor protocol code	236252

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03621046
WHO universal trial number (UTN)	U1111-1204-4692

Notes:

Sponsors

Sponsor organisation name	Aston University
Sponsor organisation address	Aston Triangle, Birmingham, United Kingdom, B4 7ET
Public contact	Research and Knowledge Exchange, Aston University, 44 01212043000, research_governance@aston.ac.uk
Scientific contact	Professor Ian Stanford, Aston University, 44 01212044015, i.m.stanford@aston.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2019
Global end of trial reached?	Yes
Global end of trial date	31 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine if a 5 mg dose of zolpidem is beneficial in reducing motor symptoms and cognitive deficits in late-stage Parkinson’s.

Protection of trial subjects:

Screening measures were used. Participants were recruited from Secondary Care Parkinson’s Disease Clinic at the Queen Elizabeth Hospital, University Hospital Birmingham NHS Foundation Trust and permitted to continue concomitant care during their participation in the trial.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	12 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 28
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8

From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment was from a single centre (Queen Elizabeth Hospital, Birmingham). All participants were recruited by the Clinical Lead (Dr Benjamin Wright) from Neurology clinics held at Queen Elizabeth Hospital, UK.

Pre-assignment

Screening details:

Diagnosis of idiopathic Parkinson’s and Hoehn and Yahr score of 2.5 or more;
Willing to participate and refrain from driving whist taking zolpidem/placebo;
Within age range 40 to 80 years.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Packaging was undertaken by the drug supplier. The placebo was over encapsulated to ensure that zolpidem and placebo capsules appeared identical. Sharp Clinical Services (UK) Ltd provided 28 containers each with a randomised label. Each container contained either 4 zolpidem or 4 placebo capsules. In addition they provided 2 sets of code breaks. On administering to patient each Participant was given a Unique Participant Identification Number (UPIN).

Arms

Are arms mutually exclusive?	Yes
Arm title	Zolpidem 5mg

Arm description:

Single dose capsule of 5 mg zolpidem for 4 days.

Arm type	Experimental
Investigational medicinal product name	zolpidem tartrate
Investigational medicinal product code	
Other name	stillnoct,
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5mg daily for 4 days.

Arm title	Placebo

Arm description:

Placebo 5mg daily for 4 days

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Zolpidem 5mg	Placebo
Started	14	14
Completed	14	13
Not completed	0	1
Consent withdrawn by subject	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Zolpidem 5mg
Reporting group description:	
Single dose capsule of 5 mg zolpidem for 4 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo 5mg daily for 4 days	

Reporting group values	Zolpidem 5mg	Placebo	Total
Number of subjects	14	14	28
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	3	7
From 65-84 years	10	11	21
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	6	10	16
Male	8	4	12

End points

End points reporting groups	
Reporting group title	Zolpidem 5mg
Reporting group description:	
Single dose capsule of 5 mg zolpidem for 4 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo 5mg daily for 4 days	

Primary: Change in UPDRS III	
End point title	Change in UPDRS III
End point description:	
A UPDRS motor Examination (Part III) was undertaken as part of the initial clinical assessment in the clinic on day 1. Following this, zolpidem or placebo was administered and the UPDRS III was repeated a minimum of 1 hour later. Post-hoc analysis confirmed a significant symptomatic improvements following administration of zolpidem (UPDRS III reduction -7.2 ± 2.37, p < 0.0001). Following administration of placebo, there was a significant reduction in UPDRS III (-8.43 ± 2.03, p < 0.0001) which was not significantly different from that found in zolpidem, p = 0.7).	
End point type	Primary
End point timeframe:	
Duration of study	

End point values	Zolpidem 5mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Change in UPDRS III				
arithmetic mean (standard deviation)	-7.21 (± 8.88)	-8.43 (± 7.59)		

Attachments (see zip file)	MeanUPDRSscore/Zolpidem t-test.pdf

Statistical analyses

Statistical analysis title	unpaired t-test
Comparison groups	Zolpidem 5mg v Placebo
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.7 [1]
Method	t-test, 2-sided

Notes:

[1] - No significant difference between zolpidem and placebo with regard to changes in UPDRS III

Primary: Correlation analysis

End point title	Correlation analysis

End point description:

Correlation analysis showed that the greatest reductions in UPDRS III were found in those patients who had exhibited the greatest deficits. Thus, the largest reduction in UPDRS III was significantly correlated, not only with initial total UPDRS ($p < 0.001$) but also with initial UPDRS III ($p < 0.01$).

However, unlike the zolpidem data, no significant correlations were found in UPDRS III improvement with either initial total UPDRS or initial UPDRS III.

End point type	Primary

End point timeframe:

Duration of trial

End point values	Zolpidem 5mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Correlation analysis				
number (not applicable)	14	14		

Attachments (see zip file)	Correlations.pdf

Statistical analyses

Statistical analysis title	Correlation

Statistical analysis description:

A comparision of UPDRS total and UPDRS III against the change in UPDRS III in Zolpidem

Comparison groups	Zolpidem 5mg v Placebo
Number of subjects included in analysis	28
Analysis specification	Post-hoc
Analysis type	other
P-value	≤ 0.001 [2]
Method	Regression, Linear
Parameter estimate	Slope

Notes:

[2] - The largest reduction in UPDRS III was significantly correlated, not only with initial total UPDRS ($p < 0.001$) but also with initial UPDRS III ($p < 0.01$).

Post-hoc: Category naming test

End point title	Category naming test

End point description:

Following administration of zolpidem, three patients showed an improved performance and nine patients showed a decline in performance with one patient showed no change (mean -2.14 ± 1.47). For placebo, five patients showed improvements and nine patients a decline and one patient no change (mean = -0.58 ± 0.89). Overall, there was no significant difference between placebo or zolpidem in the category naming test. The decline in performance after administration of zolpidem is difficult to reconcile but may be due to residual drowsiness or may just be attributable to tiredness over the course of a long day.

End point type	Post-hoc

End point timeframe:
Duration of study

End point values	Zolpidem 5mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Change in category naming				
arithmetic mean (standard deviation)	-2.14 (± 5.51)	-.58 (± 3.33)		

Attachments (see zip file)	Category naming sheet.pdf Letter Fluency Test and Category Naming Test Raw Data.pdf

Statistical analyses

No statistical analyses for this end point

Post-hoc: Letter Fluency Test

End point title	Letter Fluency Test

End point description:

Following administration of zolpidem, five patients showed improvement and nine patients showed a decline (mean = -1.39 ± 0.86). For placebo, nine patients showed improvements, three patient showed a decline and two patients no change. Overall, there was an improvement in letter fluency following placebo (1.61 ± 0.74). This is a surprising result and may indicate a learning effect or simply that the patients are more at ease upon repeating the test.

End point type	Post-hoc

End point timeframe:
Overall study

End point values	Zolpidem 5mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	14		
Units: Change in letter fluency				
arithmetic mean (standard deviation)	-1.39 (± 3.20)	1.66 (± 2.78)		

Attachments (see zip file)	Letter Fluency Test and Category Naming Test Raw Data.pdf Letter fluency sheet.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Within 24 hours of the investigator’s knowledge of occurrence	
Adverse event reporting additional description:	
Adverse effects (AEs) were assessed in the clinic (day 1) and also during telephone conversions which took place on days 2, 6 and 8	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1

Reporting groups	
Reporting group title	Zolpidem 5mg
Reporting group description:	
Single dose capsule of 5 mg zolpidem for 4 days.	
Reporting group title	Placebo
Reporting group description:	
Placebo 5mg daily for 4 days	

Serious adverse events	Zolpidem 5mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 14 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Zolpidem 5mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 14 (85.71%)	1 / 14 (7.14%)	
Social circumstances			
Anxiety	Additional description: Anxiety related to using the Smartphone		
alternative dictionary used: Sponsor definition 1			
subjects affected / exposed	0 / 14 (0.00%)	1 / 14 (7.14%)	
occurrences (all)	0	1	
Product issues			
Transient effects	Additional description: Sleeping, tiredness drowsiness (usually <1hr in duration) and/or vivid dreaming		
alternative dictionary used: Sponsor's definition 1			

subjects affected / exposed occurrences (all)	12 / 14 (85.71%) 26	0 / 14 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2019	Baseline blood pressure assessment added.
04 September 2019	Change of Chief Investigator.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported