CLINICAL TRIAL OF AN INVESTIGATIONAL MEDICINAL PRODUCT (CTIMP)

EMA RESULTS REPORT – SUMMARY

1. Details of Chief Investigator

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2. Details of study

Full title of study:	The role of Buspirone in attenuating Levodopa-induced Dyskinesias in patients with Parkinson's disease
Name of main REC:	Northampton NRES Committee – East Midlands
REC reference number:	14/EM/1309
Date of favourable ethical opinion:	12 Jan 2015
Sponsor:	Imperial College London/Imperial College Healthcare NHS Trust
Funder:	The Michael J Fox Foundation for Parkinson's Research (USA)
EudraCT Number:	2014-005422-35

3. Study design and decision plan according to the Funder

This study consists of three consecutive arms: *(i) acute clinical trial with Buspirone*, *(ii) PET imaging arm and (iii) chronic clinical trial with Buspirone*.

The study has secured funds for conducting only the acute clinical study (the Michael J Fox Foundation for Parkinson's Research, USA). Funding for the acute clinical study only was decided following a discussion with the MJF Foundation due to the fact that the PET imaging arm and the chronic clinical trial will both depend on the outcome of the acute clinical trial.

In particular, positive results in the acute clinical trial would condition the excecution of the other two arms in a go, no–go fashion. Depending on the outcome of the acute clinical study, it was agreed with MJF Foundation to make a decision using the following plan:

Possible outcomes of the acute clinical trial – Decision plan:

a. No efficacy/safety issues with either doses → acute clinical trial to terminate → no imaging study will follow

b. Efficacy with the higher dose, but not with the lower → imaging study only with the higher dose

c. Efficacy with both doses → imaging study only with the lower dose

Acute clinical trial

This is a cross-over dose-finding double–blinded trial with Buspirone 0.10mg/kg or Buspirone 0.20mg/kg and Placebo added to L-dopa.

20 PD patients have been approached for the acute clinical trial. 10 PD patients did not fulfill one or more of the exclusion criteria. 2 eligible PD patients finally decided not to take part in the study. 8 PD patients with LIDs (3M:5F) participated in the acute clinical trial. At Visit 1, all participants received Buspirone either 0.10mg/kg or 0.20mg/kg prior to L-dopa. All participants also received Placebo prior to L-dopa.

Safety of Buspirone

6 out of 8 reported mild drowsiness, fatigue and/or headache following the administration of the study drug. Patients were monitored for the next following hours at our outpatient clinical facility according to the research protocol. Adverse effects were reported immediately to the PI (Prof Paola Piccini) and were assessed as minor adverse effects possibly related to the study procedures. Patients were all fine at the end of the clinical examinations and were discharged. The PI and the clinician in charge decided not to treat any of these AEs as they were mild and released within a couple of hours without any treatment. In addition, all patients were contacted 24 hours afterwards and a week later. No further adverse events were reported.

Efficacy of Buspirone

During a routine monitoring visit from the Sponsor it was discussed whether to perform an interim analysis to assess the efficacy of Buspirone in order to apply for extending the recruitment period. It was agreed that the unblinded clinician would perform the interim analysis of collected data (N=8 participants) and the PI to make a decision using the following plan:

Possible outcomes of the interim analysis of the acute study – Decision plan:

i. No efficacy → To terminate the acute clinical trial and subsequently → to early terminate the study.

ii. Statistically significant differences between Buspirone and Placebo treatments → To include 1–2 new recruiting sites and apply for extension in the recruitment period → consider alternative funding sources.

The severity of dyskinesias was assessed using the Abnormal Involuntary Movement Scores (AIMS) scores according to the Protocol procedures outlined for Visit 1. Individual average scores of AIMS after Buspirone (either 0.10mg/kg or 0.20mg/kg) were compared to individual AIMS scores after Placebo using the parametric *paired* t-test (a=0.05).

Results of Interim Analysis

The clinical characteristics and results are summarised in the Table below.

PD patients with LIDs had similar AIMS scores whilst on Buspirone (either 0.10 or 0.20 mg/kg) as compared to Placebo ($p>0.10$). UPDRS–Part III scores (motor component of Parkinsonian symptoms and signs) and UPDRS–total scores were not statistically different when patients were rated whilst on Buspirone (either 0.10mg/kg or 0.20mg/kg) and levodopa as compared to when they were rated whilst on Placebo and levodopa ($p>0.10$).

Table – Clinical characteristics of 8 subjects who completed the acute study with Buspirone.
The values below represent means ± 1 SD. Comparisons between the Buspirone and the Placebo treatment arms were performed using the parametric paired t test.

A.

No. of participants	8
Sex	3M:5F
Age (years)	67.99±7.64
Weight (kg)	69.64±9.15
DD_{diagn} (years)	9.78±4.88
Duration on DA medication (years)	8.44±4.65
Daily LED_{Total} (mg)	591.29±262.01
MMSE score	27.88±1.73
HAM–D score	5.25±2.43
HAM–A score	8.25±5.80
BAI	10.50±5.88
H&Y stage	2.50±0.38
Schwab & England (%)	80±7.56

DD: disease duration; DA: dopaminergic; LED: levodopa equivalent dose; MMSE: mini mental state examination; HAM–D: Hamilton scale for depression; HAM–A: Hamilton scale for anxiety; BAI: Beck's anxiety inventory; H&Y: Hoehn and Yahr; AIMS: abnormal involuntary movements scale; UPDRS: unified Parkinson's disease rating scale;
[1] paired t-tests between "*off* and "*on"* dopaminergic medication states".

B.

	Placebo (+levodopa)	Buspirone total (+levodopa)		Buspirone 0.10mg/kg (+levodopa)	Buspirone 0.20mg/kg (+levodopa)		
No. of participants	8	8	p value[1]	4	4	p value[2]	p value[3]
AIMS scores	5.82±5.29	5.56±3.84	0.813	6.37+4.38	4.75+3.14	0.731	0.523
UPDRS–III	20.87±7.88	19.12±5.86	0.758	18.5+5.46	19.75+7.32	0.351	0.891
UPDRS total	41.37±10.66	40.37±7.59	0.466	40.5+7.59	40.25+8.77	0.921	0.362

The values above represent means ± 1 SD.

[1] paired t-test between Placebo (+levodopa) and Buspirone total (+levodopa) / N=8
[2] paired t-test between Placebo (+levodopa) and Buspirone 0.10 mg/kg (+levodopa) / N=4
[3] paired t-test between Placebo (+levodopa) and Buspirone 0.20 mg/kg (+levodopa) / N=4

Conclusions

Buspirone at either 0.10mg/kg or 0.20mg/kg when administered prior to levodopa did not improve individual dyskinesia scores (as shown by AIMS scale) as compared to Placebo administration in 8 patients. It was thought that even by increasing the number of subjects the final results were not likely to change. On the bais of this data it was decided to terminate the study.

I certify that the statements herein are true, complete and accurate to the best of my knowledge.

CHIEF INVESTIGATOR:

Professor Paola Piccini

(e–signature)

DATE: 26 Sept 2018