Clinical Study Report

Protocol title:

Treatment of advanced Parkinson's disease with dyskinesia, with (-)-OSU6162 – a pilot study

EudraCT No: 2009-016360-37

Start 2010-03-04 and "last patient out" (global end of trial date) 2011-08-25

Signature pages for clinical study report

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: Date: 20/02/2020

Björn Holmberg, MD, PhD
Senior physician in neurology
Department of Neurology
Sahlgrenska University Hospital
SE 413 45 Gotheburg, Sweden
Responsible investigator

Signed: Date: 19/02/2020

Radu Constantinescu, MD
Senior physician in neurology
Department of Neurology
Sahlgrenska University Hospital
SE 413 45 Gothenburg, Sweden
Responsible investigator

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TITLE PAGE

Study title: Treatment of advanced Parkinson's disease with dyskinesia with (-)-OSU6162 – a pilot study

Name of Test Drug: The substance is the S enantiomer with the chemical name (S)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride ((-)-OSU6162)

Indication studied: Parkinson´s disease with dyskinesia

Study description: Phase IIa, double-blind cross over placebo controlled pilot study

Sponsor:
Sahlgrenska University Hospital
Sponsor contact person: Björn Holmberg, Sahlgrenska University Hospital, SE-41345 Göteborg, Sweden.
Phone: +46-31-342 10 00 E-mail: bjorn.holmberg@neuro.gu.se

Main Financing: Arvid Carlsson Foundation, SEB Institutioner & Stiftelser, SE 405 04 Göteborg, Sweden

Protocol: PD 1/09; Treatment of advanced Parkinson's disease with dyskinesia with (-)-OSU6162 – a pilot study

Clinical Phase: Phase IIa, pilot study

Study dates: Start 2010-03-04 -"Last patient out" 2011-08-25

Responsible Investigators:

Björn Holmberg, MD, Ph.D.
Senior physician in neurology
Department of Neurology
Sahlgrenska University Hospital
SE 413 45 Göteborg, Sweden
Phone: +46-31-342 10 00

Radu Constantinescu, MD.
Senior physician in neurology
Department of Neurology
Sahlgrenska University Hospital
SE 413 45 Göteborg, Sweden
Phone: +46-31-342 10 00

GCP Statement: This study was performed in compliance with ICH Good Clinical Practise (GCP) including the archiving of essential documents.

Date of report: 2020-02-19

SYNOPSIS

NAME OF SPONSOR: Sahlgrenska University Hospital NAME OF FINISHED PRODUCT: (-)-OSU6162 N/A NAME OF ACTIVE INGREDIENT(S): (S)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride	INDIVIDUAL STUDY TABLE REFERRING TO MODULE 5 OF THE CTD Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Title of Study	Treatment of advanced Parkinson's disease with dyskinesia with (-)-OSU6162 – a pilot study		
Responsible Investigator(s)	Björn Holmberg, MD, Ph.D; Radu Constantinescu, MD.		
Study centre(s)	Department of Neurology, Sahlgrenska University Hospital, SE 413 45 Göteborg, Sweden		
Publication			
Study period	From: 2010-03-04 To: 2011-08-25 Note: The study was prematurely ended	Phase of development Phase II	Phase II
Objectives	*Primary Objective:* Primary objectives were to investigate the therapeutic effects of (-)-OSU6162 on motor function, motor complications, and quality of life, as measured by self-assessment questionnaires and by assessment of a movement disorder specialist, in patients with advanced Parkinson´s disease (PD) with dyskinesia. *Secondary Objective:* Secondary objectives were the therapeutic effects of (-)-OSU6162 on mental function, activities of daily living, and other aspects of motor function than those investigated as a primary endpoint, as measured by the self-assessment questionnaire and by assessment of a movement disorder specialist, in these same patients.		
Methodology	Double-blind cross over placebo controlled pilot study, where half of the patients start on the active drug and the other half start on placebo. Circular coated tablets for oral use of 15 mg and matching placebos were used. All patients received active drug and matching placebo. Dosage: Week 1: 15 mg x 2 (before breakfast and lunch). Week 2: 30 mg x 2. Week 3-4: 45 mg x 2. Total period of active drug treatment for each patient was 4 weeks and total treatment period was 8 weeks.		
Number of patients	Patients planned: 24 Patients screened and randomized: 8 Patients completed and analysed: 8		
Diagnosis and main criteria for inclusion	1. Patients who fulfil the British Brain Bank diagnostic criteria for definite PD (Hughes et al., 1992). 2. Long standing disease duration (more than 5 years). 3. Moderately disabling dyskinesia during at least 25% of the waking day, despite best medical treatment, defined as ≥2 points on each of the items NO 32 and 33 of the Unified Parkinson's Disease Rating Scale (UPDRS) part IV (complications of treatment)		

	(Lang et al., 1989). 4. Patient can rate ON/OFF time* and dyskinesia with at least a 66% concordance between patient and investigator/coordinator in a day in which patient experienced ON with and without troublesome dyskinesia and OFF time. * ON is defined as the condition in which the Parkinson medication works and reduces Parkinsonism. OFF is defined as the condition in which the beneficial effect of Parkinson medication is not present.
Test product, dose and mode of administration	The substance is the S enantiomer with the chemical name (S)-3-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride. The substance is a white powder and its melting point is 177-182°C Solubility in water is >2000 mg/ml. Current laboratory code used is (-)-OSU6162-HCl. INN has not yet been applied for. In this protocol (-)-OSU6162-HCl will be shortened to (-)-OSU6162. Double-blind cross over placebo-controlled pilot study, where half of the patients start with the active drug and the other half placebo. Circular coated tablets for oral use of 15 mg and matching placebos was used. Start dose was 15 mg (one tablet) twice daily (before breakfast and lunch) during 1 week with dose increase up to 30 mg twice daily during the following week. A final dose of 45 mg x 2 will be administered the last 2 weeks of the study. Dosage was individually flexible.
Duration of treatment	Total treatment period was 8 weeks. Total period of active drug treatment was 4 weeks.
Criteria for evaluation	*Primary efficacy variables*: a. ON-time without troublesome dyskinesia noted by using patient diaries. (In protocol "ON-time without dyskinesia.) b. Unified Parkinson´s Disease Rating Scale (UPDRS) part IV – rating complications of treatment. c. Parkinson´s Disease Questionnaire (PDQ-39) – rating quality of life. *Secondary efficacy variables:* d. ON-time with troublesome dyskinesia noted by using patient diaries. (In protocol "ON-time with dyskinesia.) e. Unified Parkinson´s Disease Rating Scale (UPDRS) part I-III – rating mentation, activities of daily living and motor function. f. Beck Depression Inventory II (BDI-II) *Assessment of diaries data:* Patients completed the home diary form, every 60 min., 24 hours/day for 3 consecutive days preceding each study visit, starting from visit 2. For each hour the patient noted the subjective experience of being in an ON- or OFF-state and in case of dyskinesia whether it was troublesome or not. The patient also noted hours of sleep during each 24 hours period. *Assessment of data for UPDRS, PDQ-39 and BDI-II:* Data was assessed at baseline (B1, week 0), cross-over (P1, week 4), end of treatment (P2, week 8) and follow up (B2, week 12). For more information about assessment points see Statistical methods below. *Safety variables:* Registration of Electrocardiography (ECG), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), general health, Adverse events

	(AE) and Serious adverse events (SAE) were performed every week throughout the study. Laboratory tests, measurement of Body mass index (BMI) and clinical examination were performed at baseline (B1, week 0), cross-over (P1, week 4), end of treatment (P2, week 8) and follow up (B2, week 12). Laboratory tests used: S-Folate; S-B12; S-Sodium; S-Potassium; S-Calcium; S-Fe; S-TIBC; S-Creatinine; S-Bilirubin; S-ALT; S-AST; S-ALP; S-T4 free; S-T3; S-TSH; B-Haemoglobin; B-Haematocrit (HCT); B-Erythrocyte particle concentration (EPC); B-Leucocyte particle concentration (LPC); B-Thrombocyte particle concentration (TPC); B-Basophils, B-Neutrophils, B-Lymphocytes, B-Monocytes, B-Eosinophils; Erc-MCV, Erc-MCH, Erc-MCHC; WBC; platelet count; Prolactin.
Statistical methods	*Following assessment points were used:* B1 – baseline; screening and start of treatment; week 0 P1 – cross-over; after 4 weeks of treatment P2 – end of treatment; after 8 weeks of treatment B2 – follow up; week12, 4 weeks after "end of treatment" Statistical analysis of baseline data was performed with nonparametric Wilcoxon Two-Sample Test (Mann-Whitney U-test) comparing baseline values (B1, week 0) for the two treatment groups ("osu-plac" and "plac-osu"). Outcome measures for both efficacy and safety data were subjected to crossover analyses according to Altman 1991. Treatment effect was tested by comparing the individual difference between assessment points P1 (cross-over, week 4) and P2 (end of treatment, week 8) for the two treatment groups ("osu-plac" and "plac-osu"). The analysis was performed with nonparametric Wilcoxon Two-Sample Test (Mann-Whitney U-test). Note: Analysis method noted in the clinical protocol according to point 6.7 has been modified. The analysis method suggested in the protocol is not used for cross-over analysis. A two-tailed significance level of $\alpha < 0.05$ was used throughout. GraphPad Prism 5 was used for calculations. Because the study was terminated in advance only 8 patients were investigated, leading to a very small statistical material. For some investigated variables n was even smaller due to missing values. Carry-forward of most recent value to replace missing data has not been applied. Diary data was not statistically tested for outcome due to unreliable recording in patient diaries. A close examination of the data revealed patient misunderstandings and difficulties in recording diary data. We therefore use only descriptive statistics for presentation. Individual mean time during waking hours for three consecutive days preceding each visit were calculated and plotted for the following variables: total ON-time, total OFF-time, ON-time without troublesome dyskinesia and ON-time with troublesome dyskinesia. Individual mean time sleep for three consecutive days preceding each visit was calculated and plotted.
SUMMARY CONCLUSIONS	*Efficacy Results:* No significant differences were found in baseline data for demographic characteristics or in baseline data for any of the efficacy variables.

No significant treatment effects were found for the Unified Parkinson's Disease Rating Scale (UPDRS), the Parkinson's Disease Questionnaire (PDQ-39) or the Beck Depression Inventory II (BDI-II) scale.

Results concerning safety data:
No clinically significant differences were found at baseline for safety data.
No clinically significant treatment effects were found for any of the laboratory safety variables, Electrocardiography (ECG), Systolic blood pressure (SBP) or Diastolic blood pressure (DBP).

Change in prolactin levels has been analyzed for only 3 of the completed 8 patients due to technical problems with the analyses. In all these 3 patients increases in prolactin were found after treatment with (-)-OSU6162. However, all prolactin levels stayed within normal limits.

No SAE was noted during the study.
The number of experienced AE were significantly higher after (-)-OSU6162 treatment (p=0.0018; Mann-Whitney-U test). The most frequent AE reported were: increased OFF (3/8), fatigue (2/8), increased dyskinesia (2/8) and vertigo (2/8). During (-)-OSU6162 treatment the study dose had to be reduced in 6 out of 8 patients, while a temporary dose reduction during placebo treatment was performed in 1 patient. Dose reduction most often, but not always, attenuated experienced AEs.

CONCLUSIONS

Because of the low number of completed patients it´s hard to draw any reliable conclusions from the efficacy data in this study. Unfortunately, no obvious signs of improvement after treatment with (-)-OSU6162 could be shown, except improvements in one patient reporting alleviation of hyperkinesia and better sleep during initial treatment with 15 mg x 2 of (-)-OSU6162. Dose increase above the initial 15 mg x 2 caused AEs in the majority of patients. However, concerning safety there were no SAEs or drop outs present and most of the AEs seen were mild and dose dependent. Like in earlier studies of advanced Parkinson´s disease, this study concludes that (-)-OSU6162 doses may have to be titrated from very low levels in these patients.

DATE OF THE REPORT: 2020-02-19

LIST OF ABBREVIATIONS & DEFINITION OF TERMS

AD – Abnormalities Detected

AE – Adverse Event

BDI – Beck Depression Inventory

BMI – Body Mass Index

CIOMS – Council for International Organizations of Medical Sciences

CONSORT - Consolidated Standards of Reporting Trials

CRF – Case Report Form

CTC – Clinical Trial Center

DBP – Diastolic Blood Pressure

ECG – Electrocardiography

GCP – Good Clinical Practice

ICH -International Conference on Harmonisation

LV – Läkemedelsverket. English: Swedish Medical Products Agency (MPA)

MPA – Medical Products Agency

NAD – No Abnormalities Detected

OFF – Condition in which the beneficial effect of Parkinson medication is not present

ON – Condition in which the Parkinson medication works and reduces Parkinsonism

PD – Parkinson's disease

PDQ-39 – Parkinson´s disease questionnaire 39

SAE – Serious Adverse Event

SBP – Systolic Blood Pressure

SNRI – Serotonin-noradrenaline reuptake inhibitor

SS – Sahlgrenska Universtitetssjukhuset (Sahlgrenska University hospital)

SSRI – Selective serotonin reuptake inhibitor

UPDRS – Unified Parkinson´s disease Rating Scale

VES – ventricular extrasystole

ETHICS AND REGULATORY APPROVAL

INDEPENDENT ETHICS COMMITTEE APPROVAL

The study protocol and all its amendments, and the patient information sheet(s) were reviewed and approved by the appropriate independent ethics committees as detailed in **Table 1** below.

Table 1:Ethics committees

Centre name and number	Regionala etikprövningsnämnden i Göteborg	Dnr 685-09
Investigator	Sahlgrenska University Hospital	
Ethics committee	EPN Göteborg	
Chairman	Margit Kärrström	
Date of approval of the final protocol	2010-02-06	
Date of approval of amendment 1		
Date of approval of amendment 2		
Date of approval of amendment 3		

ETHICAL CONDUCT OF THE STUDY

The trial was performed in accordance with the current version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, in October 2000) and was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practise (GCP).

PATIENT INFORMATION AND CONSENT

All patients provided written informed consent to participate in the study prior to being screened. The patient information sheet detailed the procedures involved in the study (aims, methodology, potential risks and anticipated benefits) and the investigator explained these to each patient. The patient was then allowed time to consider the information presented before signing and dating the informed consent form to indicate that they fully understood the information, and willingly volunteered to participate in the study. The patient was given a copy of the informed consent form for their information. The original copy of the informed consent was kept in a confidential file in the Investigators centre records.

REGULATORY APPROVAL

The study was performed in compliance with the requirements of the Medical Product Agency of Sweden. The study gained full regulatory approval on 2010-02-04. Sponsor was issued with the following EudraCT number **2009-016360-37**.

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Table 2: shows the principal study personnel involved in the study.

Title	Name and affiliation
Principal Investigator	Björn Holmberg, MD, PhD Senior physician in neurology Department of Neurology Sahlgrenska University Hospital SE 413 45 Gotheburg, Sweden
Principal investigator	Radu Constantinescu, MD Senior consultant in neurology Department of Neurology Sahlgrenska University Hospital SE 413 45 Gothenburg, Sweden
Sponsor	Sahlgrenska University Hospital
Sponsor contact person	Björn Holmberg, MD, PhD Senior physician in neurology Department of Neurology Sahlgrenska University Hospital SE 413 45 Gotheburg, Sweden Phone: +46-31-342 10 00
Project Leaders	Björn Holmberg, MD, PhD, Senior physician in neurology Department of Neurology Sahlgrenska University Hospital
Clinical Research Associate(s)	Filip Bergquist, MD, PhD Thordis Gudmundsdottir, MD Anke Brederlau, MD, PhD Ing-Britt Arnesen, study nurse Carina Karlberg, study nurseAll at the Department of Neurology, Sahlgrenska University Hospital, 41345 Göteborg, Sweden, phone: +46-31-3421000. Forming part of the study group were also †Arvid Carlsson and Maria Carlsson.
Laboratory investigator	Safety laboratory blood samples were analyzed at Sahlgrenska University Hospital, Göteborg, Sweden.
Data Management	Data collection in CRF: Björn Holmberg, MD, PhD Radu Constantinescu, MD, PhD Ing-Britt Arnesen, study nurse Carina Karlberg, study nurse Collation and analysis of CRF data, calculation and statistics: Angélica Kloberg, PhD, A Carlsson Research AB.

INTRODUCTION

Parkinson's disease (PD) is a common, progressively disabling neurodegenerative movement disorder, with a prevalence approaching 1% in people over 65 years old. Its most conspicuous symptom is Parkinsonism, a movement disturbance consisting of a combination of rest tremor, rigidity and hypokinesia. In addition, neuropsychiatric and cognitive symptoms such as depression, anxiety, tiredness, impaired stress tolerability and simultaneous capacity, may be present in different degrees from the very beginning and throughout the disease course. Patients with PD have reduced movement capacity, impaired activities of daily life function, decreased quality of life, increased morbidity and mortality. There is no curative or disease modifying treatment available at present. However, there is a large variety of symptomatic treatment options, including levodopa, dopamine agonists, levodopa and dopamine degrading enzyme inhibitors, anticholinergics, and other drugs.

Long-term management of PD is complicated by the emergence of response fluctuations ("wearing OFF", "ON-OFF") and motor complications such as dyskinesia and "OFF" dystonia (Fahn 2000). ON is defined as the condition in which the Parkinson medication works and reduces Parkinsonism, while OFF is defined as the condition in which the beneficial effect of Parkinson medication is not present.

These complications are, in part, a consequence of prolonged use of dopaminergic therapy, with levodopa playing a predominant role. After 4-6 years of levodopa treatment, the risk of experiencing motor fluctuations or dyskinesia has been reported to range between 8-64 % (Ahlskog et al., 2001) and at 15 years follow-up, 94% of PD patients showed dyskinesia or wearing OFF (Hely et al., 2005). Higher dosages of levodopa result in more dyskinesia and wearing-OFF, as shown in the Earlier versus later levodopa therapy in PD trial (ELLDOPA) (Fahn et al., 2004). The incidence of dyskinesia can be reduced by initiating treatment with dopamine agonists instead of levodopa (Clarke et al., 2001, The Parkinson Study Group 2004). However, both one ropinirole study and one pramipexole study showed that this was no longer the case, once levodopa was supplemented to the initial dopamine agonist monotherapy (Rascol et al., 2006, Constantinescu et al., 2007). There is no efficient treatment for dyskinesia, once they appear. The current approach is to decrease and stabilize the total dopaminergic stimulation by reducing the medication levels and minimizing drug concentration fluctuations. Due to an extremely narrow therapeutic window at this stage, reductions of medication can easily lead to the re-emergence of Parkinsonism. Amantadine can be effective in reducing dyskinesia but its usefulness is transient and limited by side effects. Severe dyskinesia together with other symptoms of advanced PD must sometimes be addressed by sophisticated pump treatments (apomorphine or Duodopa pumps) or neurosurgery, carrying a high risk for serious adverse effects. There is an unmet medical need for effective treatments for dyskinesia and for better treatment options in advanced PD.

RATIONALE FOR THE STUDY

(-)-OSU6162 belongs to a group of compounds called dopaminergic stabilizers which are candidate drugs that modulate dopaminergic transmission. (-)-OSU6162 was in early clinical studies found to inhibit L-DOPA-induced dyskinesia in patients suffering from Parkinson´s disease, without interfering with the therapeutic effects of L-DOPA (Tedroff et al. 1998). In these studies (-)-OSU6162 was well tolerated with only mild to moderate adverse events (AE) reported at oral doses above 0.5 mg/kg. The most frequent adverse events were drowsiness/sedation, dizziness, nausea and taste perversion (bitter taste).

In the present study, with the stepwise increasing dose level design and with the final dose 45 mg twice daily, mild non-serious side effects were expected. Due to its unique stabilizing properties we hypothesized that (-)-OSU6162 could alleviate symptoms caused by dopaminergic overstimulation, such as dyskinesia, but without causing deficits in dopaminergic function, and thus Parkinsonism. In this way, we expected (-)-OSU6162 to increase the time with satisfactory movement capacity without problematic dyskinesia and increase our patients' quality of life, which is the main goal of all treatment strategies in advanced PD.

STUDY OBJECTIVES

The study was conducted in order to investigate the effect of (-)-OSU6162 on motor function, activities of daily life function, dyskinesia, mental activities, quality of life, and the safety of this product in 24 patients (men and women) who suffer from advanced PD with dyskinesia.

Primary Objectives

Primary objectives were to investigate the therapeutic effects of (-)-OSU6162 on motor function, motor complications, and quality of life, as measured by self-assessment questionnaires and by assessment of a movement disorder specialist, in patients with advanced PD with dyskinesia. Specification of the self-assessment questionnaires and tests used see "EFFICACY VARIABLES" below (page 21).

Secondary Objectives

Secondary objectives were to investigate the therapeutic effects of (-)-OSU6162 on mental function, activities of daily living, and other aspects of motor function than those investigated as a primary objective, as measured by the self-assessment questionnaire and by assessment of a movement disorder specialist, in these same patients. Specification of the self-assessment questionnaires and tests used see "EFFICACY VARIABLES" below (page 21).

INVESTIGATIONAL PLAN

Double-blind cross over placebo-controlled pilot study, where half of the patients started with the active drug and the other half placebo. Circular coated tablets for oral use of 15 mg and matching placebos was used. The tablets were packed in blister packs. Total period of active drug treatment for each patient was 4 weeks and total treatment period was 8 weeks.

All patients received active drug and matching placebo. Dosage: Week 1: 15 mg x 2 (before breakfast and lunch). Week 2: 30 mg x 2. Week 3-4: 45 mg x 2.

The dosage was individually flexible. This means that if a person experienced alleviation of symptoms on a specific dose, but a dose increase resulted in decreased therapeutic effect and/or unacceptable adverse events, the lower dose was resumed and could be the final dose for that patient. This was to avoid missing a probable therapeutic window.

For more detailed design information see **Figure 1** under Overall study design and plan below, (page 16).

Randomisation

Randomisation was done externally. Procedures were taken to guarantee blinding. The code was kept in a locked drawer at the study site, Department of Neurology, Sahlgrenska University Hospital.

The packaging, labelling and coding were done by Galenica AB, Lund, Sweden. The coded packages were distributed to the Department of Neurology, Sahlgrenska University Hospital, where the study nurse or the investigator was responsible for dispensing the packages according to the randomization list to the patients. All persons dealing with the patients were blinded towards active drug or placebo.

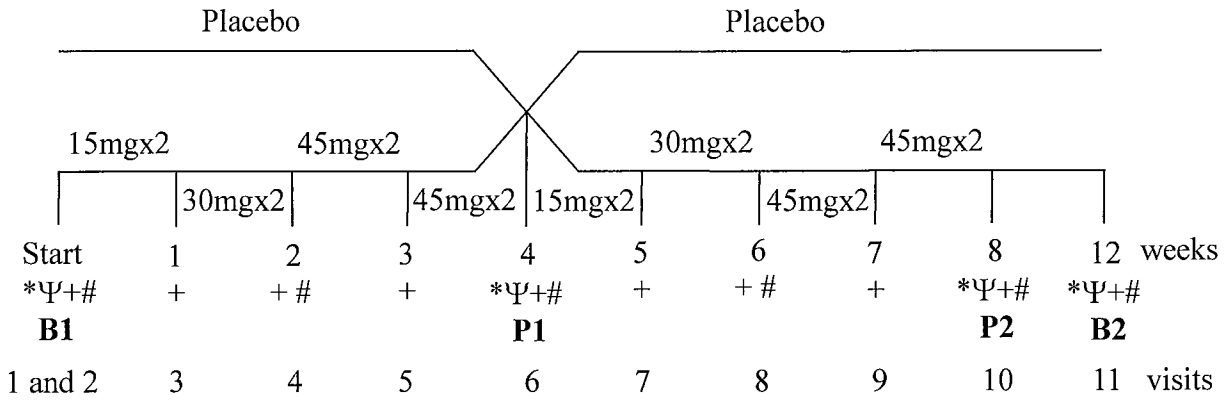
The randomization procedure was performed in agreement with CONSORT (Consolidated Standards of Reporting Trials) guidelines.

OVERALL STUDY DESIGN AND PLAN

Double-blind crossover placebo-controlled pilot study. **Figure 1** below shows a schematic presentation of the study.

Figure 1

Schematic presentation of the study design



* Laboratory (blood) examinations
Ψ Surveys and tests
\+ Consultation with study nurse
\# Consultation with neurologist; in addition one visit for inclusion
Visit 1 = screening; visit 2 = baseline /start of treatment;
visit 10 = end of treatment; visit 11 = follow up
Self-evaluation of diaries performed before each visit (from visit 2)
Blood pressure and ECG measured at each visit
B1, P1, P2 and B2 = data assessment points
B1=baseline; P1=cross-over
P2=end of treatment; B2=follow up

STUDY TIMING

Study start in March 2010. Termination of study ("last patient out") in August 2011. NOTE: The study was prematurely ended.

STUDY LOCATION

The study was conducted at the following location:

Department/Clinic of Neurology
Sahlgrenska University Hospital
SE 413 45 Göteborg, Sweden
Telephone number: +46-31-342 10 00

SELECTION OF STUDY POPULATION

INCLUSION CRITERIA

1. Participants who fulfil the British Brain Bank diagnostic criteria for definite PD (Hughes et al., 1992).
2. Long standing disease duration (more than 5 years).
3. Moderately disabling dyskinesia during at least 25% of the waking day, despite best medical treatment, defined as ≥2 points on each of the items no. 32 and 33 of the Unified Parkinson's Disease Rating Scale (UPDRS) part IV (complications of treatment) (Lang et al., 1989).
4. Patient can rate ON/OFF time and dyskinesia with at least a 66% concordance between patient and investigator/coordinator in a day in which patient experienced ON with and without dyskinesia and OFF time.

EXCLUSION CRITERIA

1. Other significant somatic or psychiatric morbidity including drug or alcohol abuse.
2. Dementia.
3. Unsatisfactory communication with the patient due to language difficulties of unsatisfactory compliance with study protocol.
4. Suspicion of an atypical parkinsonian disorder.
5. Women in fertile age who are not on contraceptives.
6. Pregnant women.

STUDY POPULATION

The study was planned for 24 patients but only 8 patients were included, started and completed. The study was prematurely ended because of dose limiting AEs.

Patients recruited from: the Clinic of Neurology at Sahlgrenska University Hospital.
Screening: 8 patients
Screening failure: 0 patients
Significant pathological lab finding from inclusion: 1 patient showed a slight abnormality on the ECG in the form of a right bundle branch block. This condition stayed unaltered throughout the study.
Concomitant medications: 8 patients
Drop-out: 0 patients
Completed: 8 patients

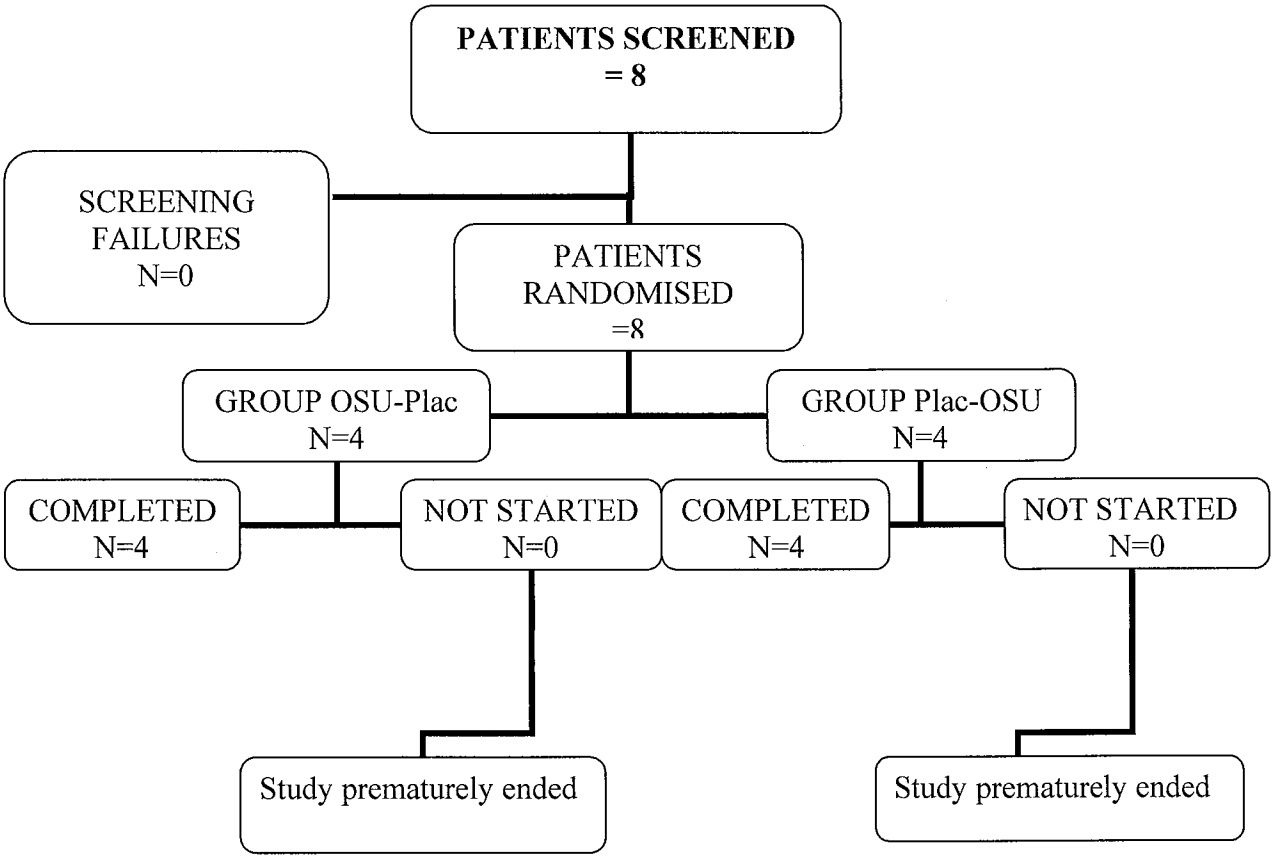
Lowered dose during placebo treatment: 1 patient

Lowered dose during (-)-OSU6162 treatment: 6 patients

Medication stops during placebo treatment: 1 patient

Medication stops during (-)-OSU6162 treatment: 3 patients

Figure 2



WITHDRAWAL OF PATIENTS FROM THERAPY OR ASSESSMENT

Patients were free to withdraw from the study at any time without giving a reason. Patients were advised that if they requested to withdraw from the study, at any time during the trial, then this would have no negative consequences. The investigator could also withdraw patients from the trial if they deemed it appropriate for safety or ethical reasons or if it was considered to be to be detrimental to the well-being of the patient. There were no withdrawals in this study.

TREATMENTS

Double-blind cross over placebo-controlled pilot study, where half of the patients started with the active drug and the other half placebo. Circular coated tablets for oral use of 15 mg and matching placebos was used. Tablets were packed in blister packages.

TREATMENTS ADMINISTERED

The tablets were administered by research nurses at the Department of Neurology, Sahlgrenska University Hospital, SE 413 45 Göteborg, Sweden

DESCRIPTION OF INVESTIGATIONAL PRODUCTS

The active substance was the S enantiomer with the chemical name (S)-3-[3-(methylsulfonyl) phenyl]-1-propylpiperidine hydrochloride. The substance is a white powder and its melting point is 177-182°C Solubility in water is > 2000 mg/ml. Current laboratory code used is (-)-OSU6162-HCl. INN has not yet been applied for. In the protocol (-)-OSU6162-HCl was shortened to (-)-OSU6162. Active substance was manufactured by Syntagon AB, Södertälje, Sweden.
(-)-OSU6162 belongs to a group of compounds called dopaminergic stabilizers which are candidate drugs that modulate dopaminergic transmission.

DOSES USED IN THE STUDY

Start dose was 15 mg x 2 (in the morning and at lunch) during week 1 with dose increase up to 30 mg x 2 during the following week in each study period. A final dose of 45 mg x 2 was administered the last 2 weeks in each study period. Total period for active drug treatment for each patient was 4 weeks.

SELECTION AND TIMING OF DOSE FOR INDIVIDUAL PATIENTS

The dosage was individually flexible. This means that if a person experienced alleviation of symptoms on a specific dose, but a dose increase resulted in decreased therapeutic effect and/or unacceptable adverse

events, the lower dose was resumed and could be the final dose for that patient. This was to avoid missing a probable therapeutic window.

PRIOR AND CONCOMITANT THERAPY

Medication that was permitted included acetyl salicylic acid, lipid or blood pressure lowering medication, antidepressants, PD medication including: levodopa, dopamine agonists, anticholinergics, COMT-inhibitors, MAO-B inhibitors. Medications not permitted included glutamate inhibitors (amantadine), neuroleptics, reserpine, anti-epileptics (with the exception of gabapentin). At baseline all antiparkinsonian treatment had to have been stable for at least 4 weeks.

Table 3: Concomitant medication

Concomitant medication	**Number of patients**	**Concomitant medication**	**Number of patients**
Sifrol	5	Folacin	2
Madopark (depot/Quick/Quick mite)	7	Calcichew/Alenat	1
Sinemet depot mite	3	Omega-3	1
Stalevo	4	Trombyl/Waran	1/1
Azilect	5	Ibumetin/Panocod/Panodil/Citodon	4
Comtess	1	Detrusitol	1
Levodopa/Carbidopa	2	Motilium	1
Apo Go pen (syringe)	2	Movicol	1
Neupro depot-patch	2	Ebixa	1
Mirtazapin	1	Enalapril/Alfadil	1/1
Orstanorm	1	Zopiklon	1
Levaxin	2	Xanor	1
Behepan/Betolvidon	1/2	Artrox	1

ACCOUNTABILITY

The study drug was kept in a secure place and was supplied to patients by the supervising study nurse/physician. The investigator maintained records of the dispensing of the study drugs. Any study drug accidentally or deliberately destroyed was accounted for. Any discrepancies between amounts dispensed and returned was explained and noted in the CRF.

Containers were destroyed by the Pharmacy at Sahlgrenska University Hospital after study ending.

EFFICACY AND SAFETY VARIABLES

EFFICACY VARIABLES

I. Primary efficacy variables:

Effects of treatment with (-)-OSU6162 in advanced PD were measured as the individual difference between assessment point P1 (cross-over point *) and P2 (end of treatment *) for the two treatment groups ("osu-plac" and "plac-osu"; see **Figure 1**) in variables studying motor function, motor complications, and quality of life. Note: Analysis method noted in the clinical protocol according to point 6.7 has been modified. The analysis method suggested in the protocol is not used for cross-over analysis.

The following assessments were made:

a. ON-time without troublesome dyskinesia (patient diaries). Note: In protocol this variable is defined as: ON-time without dyskinesia (patient diaries).
b. Unified Parkinson's Disease Rating Scale (UPDRS) part IV (complications of treatment).
c. Parkinson's Disease Questionnaire (PDQ-39) (Peto et al., 1995) (quality of life).

II. Secondary efficacy variables:

Effects of treatment with (-)-OSU6162 in advanced PD were measured as the individual difference between assessment point P1 (cross-over point *) and P2 (end of treatment *) for the two treatment groups ("osu-plac" and "plac-osu"; see **Figure 1**) in variables studying mental function, motor function, activities of daily living, and depressivity. Note: Analysis method noted in the clinical protocol according to point 6.7 has been modified. The analysis method suggested in the protocol is not used for cross-over analysis.

The following assessments were made:

d. ON-time with troublesome dyskinesia (patient diaries). Note: In protocol this variable is defined as: ON-time with dyskinesia (patient diaries).
e. Unified Parkinson's Disease Rating Scale (UPDRS) part I-III (mentation, activities of daily living and motor function, respectively).
f. Beck Depression Inventory II (BDI-II).

Assessment of diaries data:

Patients completed the home diary form, every 60 min., 24 hours/day for 3 consecutive days preceding each study visit, starting from visit 2. For each hour the patient noted the subjective experience of being in an ON- or OFF-state and in case of dyskinesia whether it was troublesome or not. The patient also noted hours of sleep during each 24 hours period.

Assessment of data for UPDRS, PDQ-39 and BDI-II:

Data for the scales UPDRS, PDQ-39 and BDI-II was assessed at baseline (B1*), cross-over (P1*), end of treatment (P2*) and follow up (B2*).

The UPDRS evaluations were performed by the same neurologist for every particular patient, at about the same time of the day, between one to two hours after anti-parkinsonian medication intake, either in the morning, after breakfast, or in the afternoon, after lunch. Patients were in the defined ON state.

SAFETY VARIABLES

The following measurements were performed and statistically analyzed:

a) Measurement of Electrocardiography (ECG), Systolic blood pressure (SBP) and Diastolic blood pressure (DBP) were performed every week throughout the study during consultation with the study nurse or neurologist. At all these visits general health was noted and the patient was asked for any additional symptoms during the past week. Possible signs of Adverse events (AE) or Serious adverse events (SAE) were noted.
b) Laboratory tests, Body mass index (BMI) and clinical examination were performed at baseline (B1, *), cross over point (P1*), end of treatment (P2*) and follow up (B2*).

Laboratory tests included:

S-Folate; S-B12; S-Sodium; S-Potassium; S-Calcium; S-Fe; S-TIBC; S-Creatinine; S-Bilirubin; S-ALT; S-AST; S-ALP; S-T4 free; S-T3; S-TSH; B-Haemoglobin; B-Haematocrit (HCT); B-Erythrocyte particle concentration (EPC); B-Leucocyte particle concentration (LPC); B-Thrombocyte particle concentration (TPC); B-Basophils, B-Neutrophils, B-Lymphocytes, B-Monocytes, B-Eosinophils; Erc-MCV, Erc-MCH, Erc-MCHC; WBC; platelet count; Prolactin.

c) Consultations with neurologist were performed at baseline (B1*); after 2 weeks of treatment; cross over point (P1 *); after 6 weeks of treatment; at end of treatment (P2 *) and at follow up (B2 *).

*For more information about the definitions of assessment points in the study schedule see **Figure 1**: "Schematic presentation of the study design", under OVERALL STUDY DESIGN AND PLAN (page 16).

REPORTING OF AE/SAE

An AE/SAE is any worsening of an undesirable or unintended sign, symptom (including an abnormal laboratory finding), or disease that is temporally associated with the use of (-)-OSU6162 whether considered related to the medicinal product or not.

Spontaneous reporting by the patients and active questioning was used. The patients got telephone numbers to the clinic responsible for the trial and mobile phone numbers to the responsible investigator. Medical examination of general health including routine blood sample examination, ECG analysis and measurement of blood pressure were performed continuously throughout the study including follow-up (see **Figure 1**, page 16).

STATISTICAL ANALYSES

Statistical analysis of baseline data was performed with nonparametric Wilcoxon Two-Sample Test (Mann-Whitney U-test) comparing baseline values (B1, week 0) for the two treatment groups ("osu-plac" and "plac-osu").
Outcome measures for both efficacy and safety data were subjected to cross-over analyses according to Altman 1991. Treatment effect was tested by comparing the individual difference between assessment points P1 (cross-over) and P2 (end of treatment) for the two treatment groups ("osu-plac" and "plac-osu"). The analysis was performed with nonparametric Wilcoxon Two-Sample Test (Mann-Whitney U-test).
A two-tailed significance level of $\alpha < 0.05$ was used throughout. GraphPad Prism 5 was used for calculations. Note: Analysis method noted in the clinical protocol according to point 6.7 has been modified. The analysis method suggested in the protocol is not used for cross-over analysis.

Analysis of diaries data

Diary data was not statistically tested due to unreliable recording in patient diaries. A close examination of the data revealed patient misunderstandings and difficulties in recording diary data. We therefore use only descriptive statistics for presentation. Individual mean time during waking hours for three consecutive days preceding each visit were calculated and plotted for the following variables: total ON-time, total OFF-time, ON-time without troublesome dyskinesia and ON-time with troublesome dyskinesia. Individual mean time sleep for three consecutive days preceding each visit was calculated and plotted.
Note that the primary and secondary efficacy variables concerning the variable dyskinesia were calculated in a different manner than specified in the clinical protocol. According to protocol: Primary efficacy variable - ON-time without dyskinesia; Secondary efficacy variable - ON-time with dyskinesia. In patients with advanced Parkinson´s disease dyskinesia is almost always present during ON-time. It is therefore important to be able to distinguish between ON-time with troublesome dyskinesia and ON-time without troublesome

dyskinesia. The aim of the treatment is to increase ON-time without troublesome dyskinesia. In the diary instructions used, patients were therefore instructed to specify the presence of troublesome dyskinesia and not troublesome dyskinesia.

Handling of drop outs or missing data

There were no drop outs in this study. However, because the study was terminated in advance only 8 patients were investigated, leading to a very small statistical material. For some investigated variables n was even smaller due to missing values. Carry-forward of most recent value to replace missing data has not been applied.

RESULTS

DEMOGRAPHIC BASELINE CHARACTERISTICS

Table 4. Demographic baseline characteristics. Shown are quantity or median (range)

	Started with (-)-OSU6162	**Started with placebo**
Number of persons who completed study	4	4
Gender Female/Male	0F/4M	1F/3M
Age	67 (59-78)	63 (42-75)
Weight (kg)	71.5 (53-102)	69.3 (55-78)
Body mass index (kg/m^2)	23.3 (20.4-30.8)	21.4 (20-22.3)
SBP (systolic blood pressure)	125 (105-200)	140 (95-150)
DBP (diastolic blood pressure)	77.5 (65-110)	75 (65-95)

No statistically significant differences were found in demographic baseline characteristics.

EFFICACY RESULTS

PATIENT DIARIES RESULTS

Mean time during waking hours for the variables: total ON-time, total OFF-time, ON-time without troublesome dyskinesia and ON-time with troublesome dyskinesia have been calculated for each patient and visit and are plotted in **Figure 3a-d. Figure 3e** shows individual mean time sleep preceding each visit.
Figure definitions: Visit 2 = baseline (B1)/start of treatment; visit 6 = cross-over point (P1); visit 10 = end of treatment (P2); visit 11 = follow up (B2). Black curves represent patients in the group "plac-osu" and red curves patients in the group "osu-plac".

Figure 3a

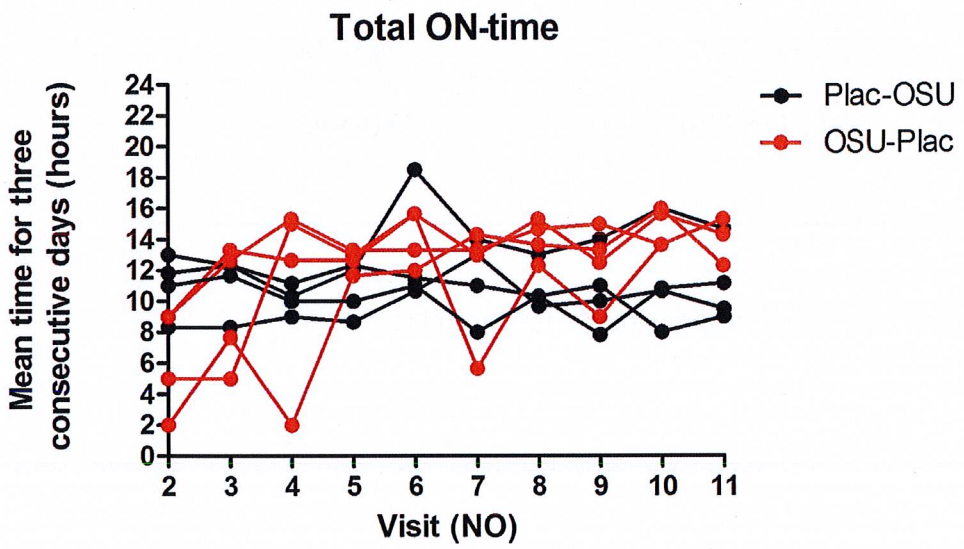


Figure 3b

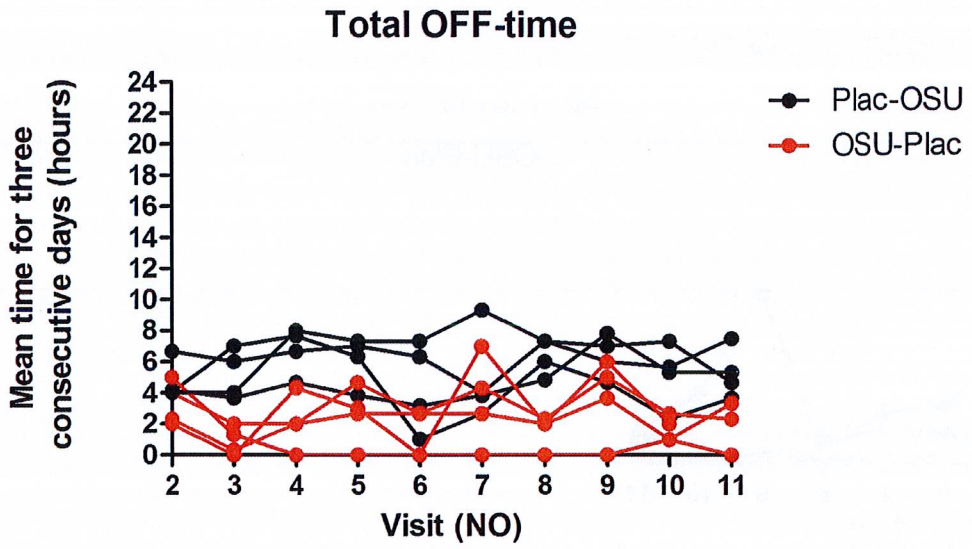


Figure 3c

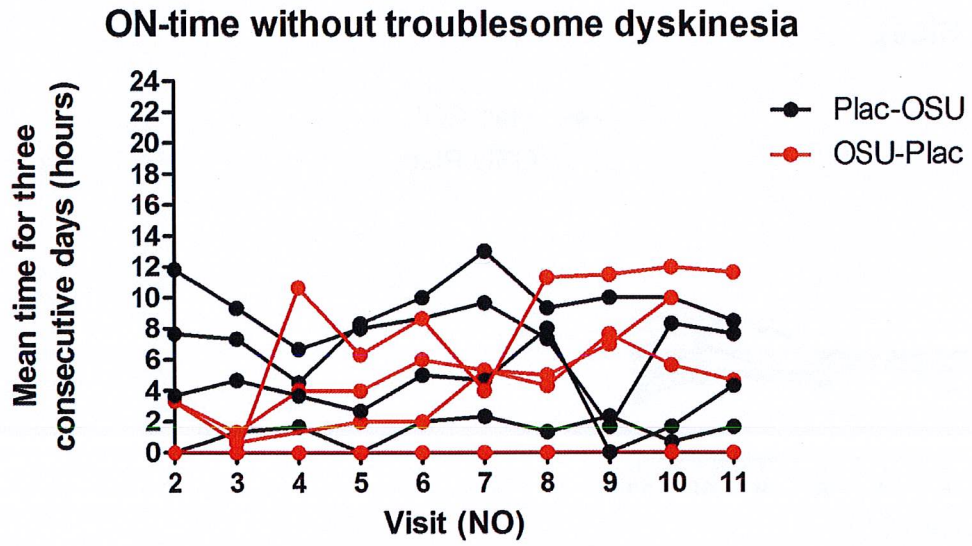


Figure 3d

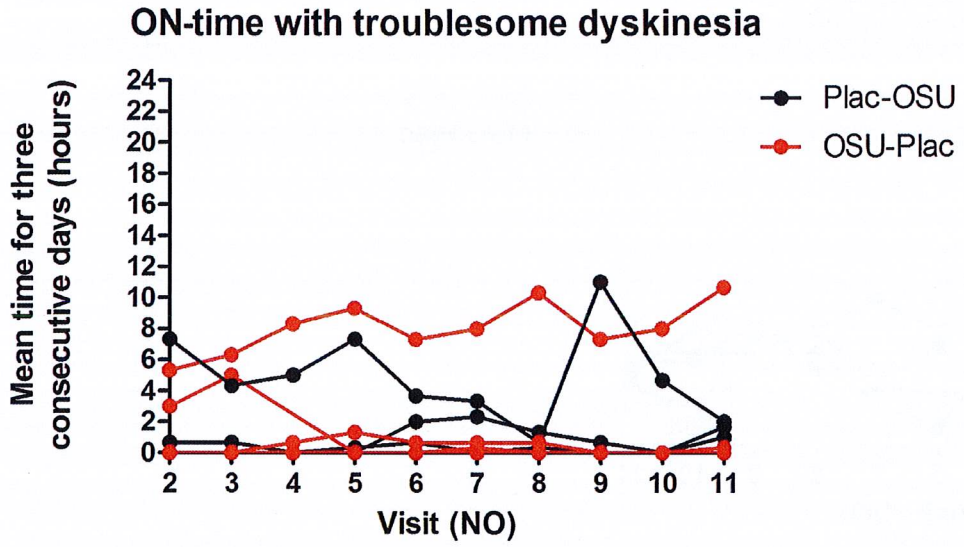
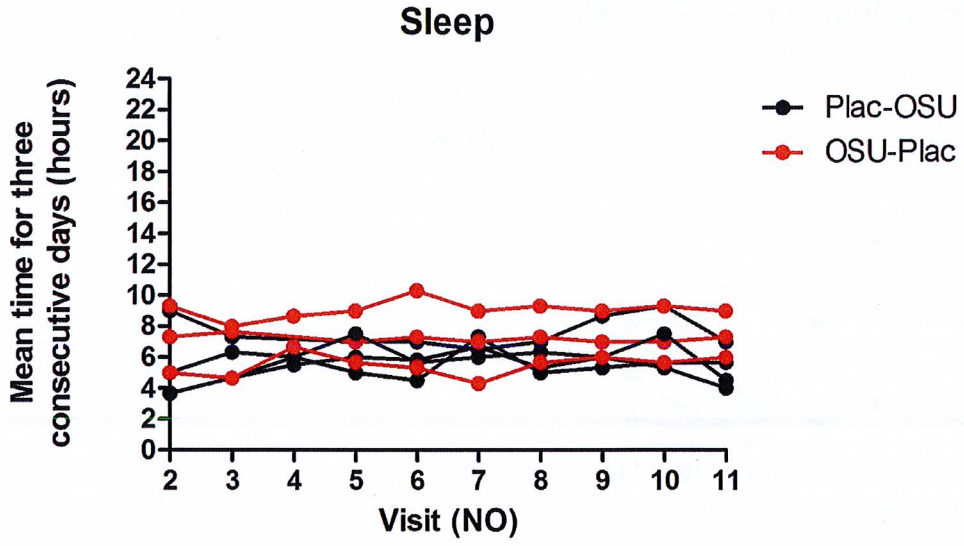


Figure 3e



Diary data was not statistically tested due to unreliable recording in patient diaries. A close examination of the data revealed patient misunderstandings and difficulties in recording diary data. We therefore use only descriptive statistics for presentation in **Figure 3**. Total OFF-time plots show separation of the groups, where patients in the "plac-osu" group have more time with OFF throughout the study. ON-time with troublesome dyskinesia was continuously present in two patients and partly present in another two patients during the study.

UPDRS RESULTS

No statistically significant differences between intervention groups were found in UPDRS baseline data.

No statistically significant treatment effects were found for the UPDRS I-IV scales. Individual UPDRS I-IV score values for the assessment points B1, P1, P2 and B2 are shown in **Figure 4a-d.** Black curves represent patients in the group "plac-osu" and red curves patients in the group "osu-plac". In the UPDRS scales a low value is desirable.

Figure 4a

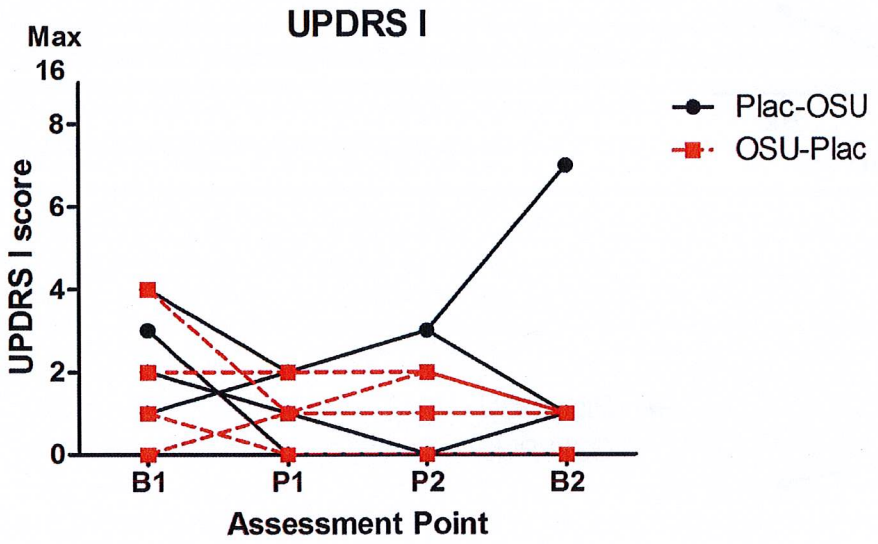


Figure 4b

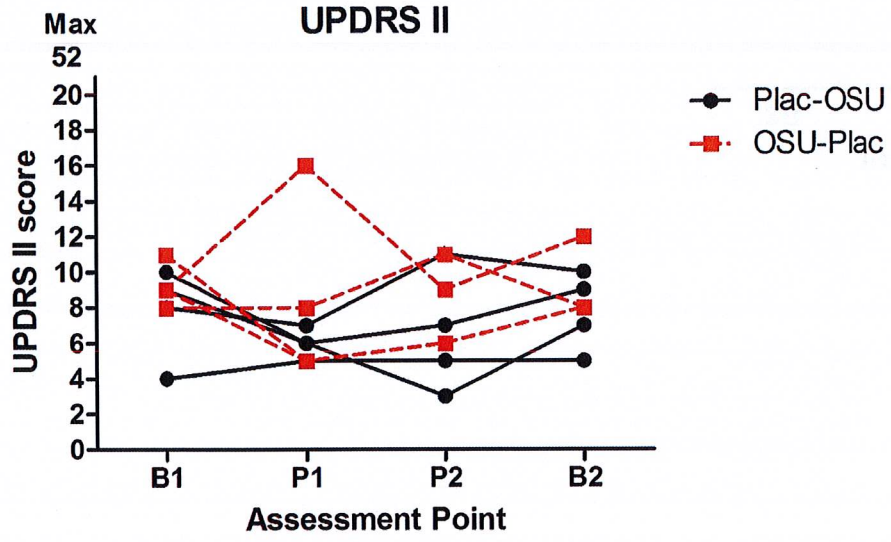


Figure 4c

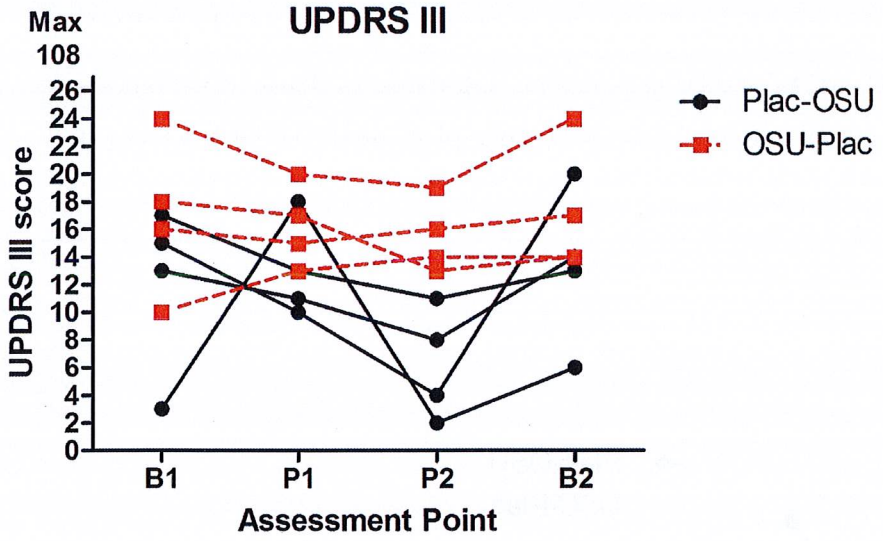
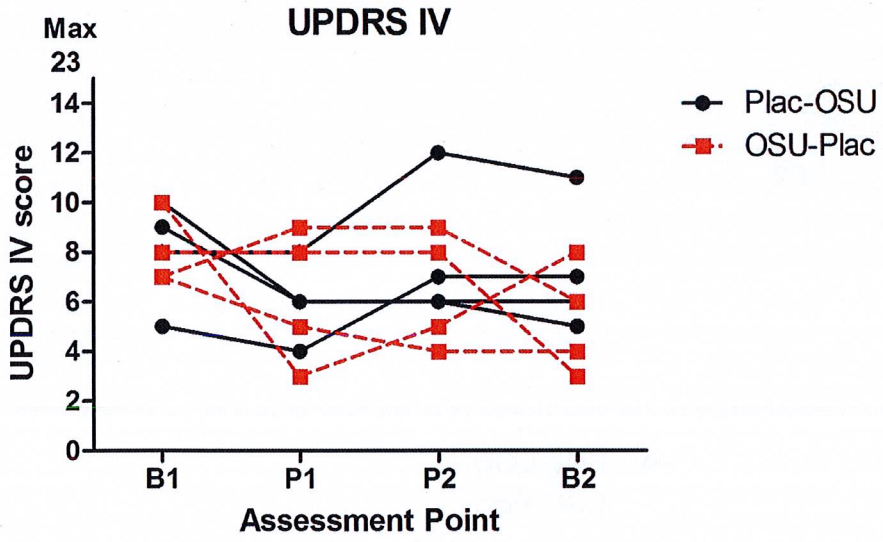


Figure 4d



In **Figure 5a-d** the mean (with SEM - standard error of the mean) change in UPDRS I-IV score values between the assessment points B1, P1 and P2 are shown for the two treatment groups "osu-plac" (red curve) and "plac-osu" (black curve). Note that only assessment points P1 and P2 have been used for statistical testing of treatment effect.

Figure 5a

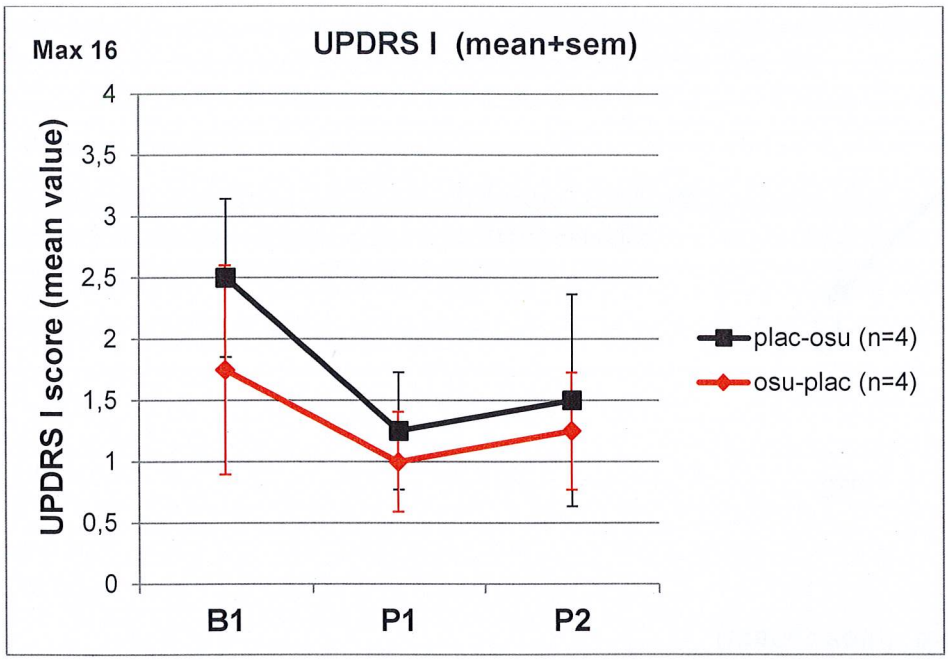


Figure 5b

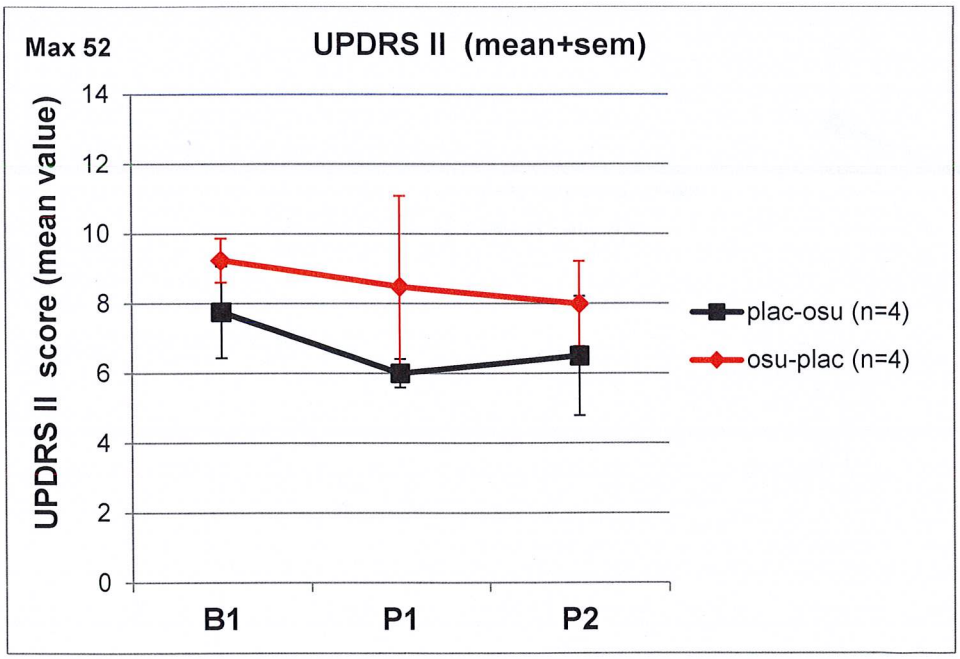


Figure 5c

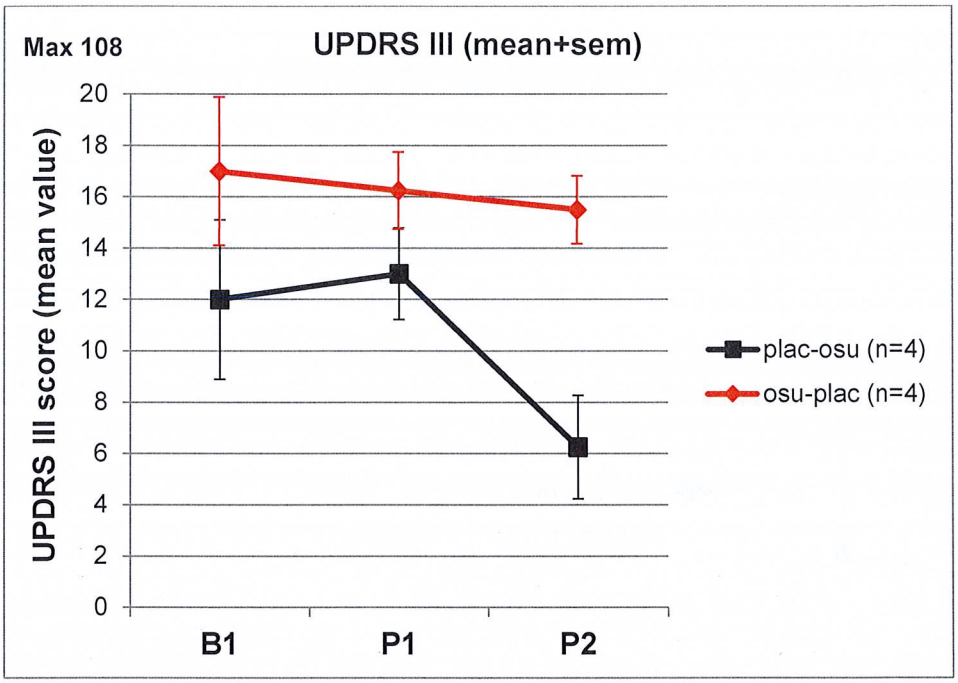
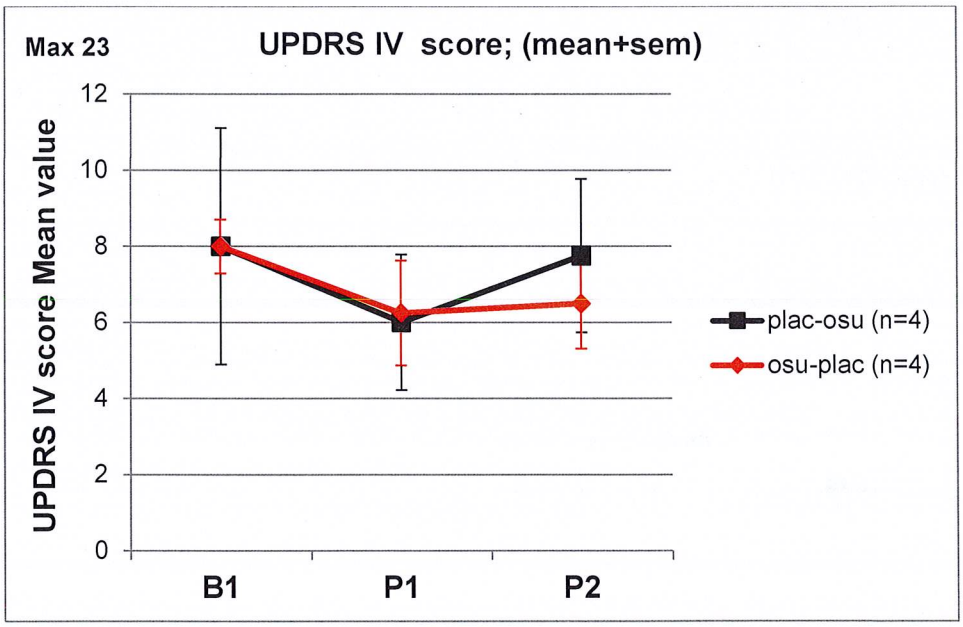


Figure 5d



PDQ-39 RESULTS

No statistically significant differences between intervention groups were found in PDQ-39 baseline data.

No statistically significant treatment effects were found for the PDQ-39 quality of life scale. Individual PDQ-39 score values for the assessment points B1, P1, P2 and B2 are shown in **Figure 6a-h**, below. Black curves represent patients in the group "plac-osu" and red curves patients in the group "osu-plac". In the PDQ-39 scales a low % value is desirable.

Figure 6a

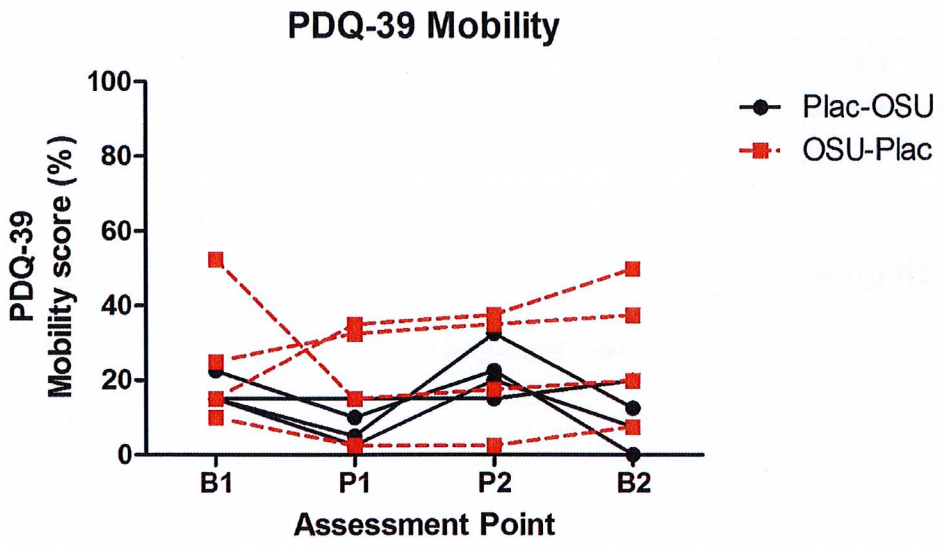


Figure 6b

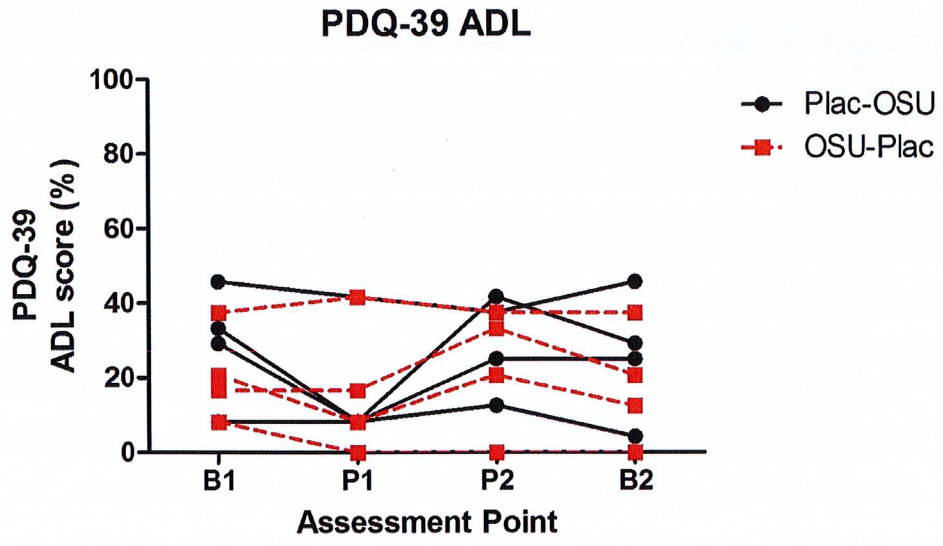


Figure 6c

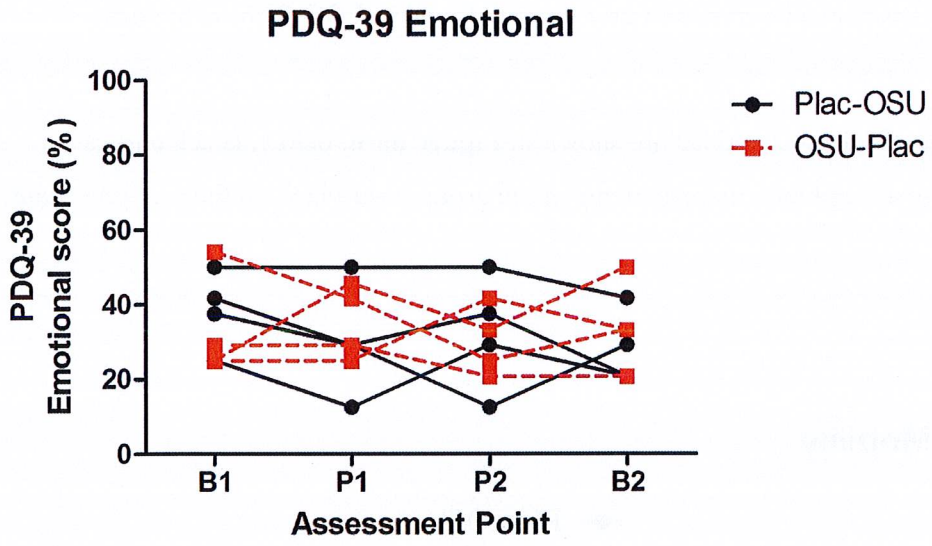


Figure 6d

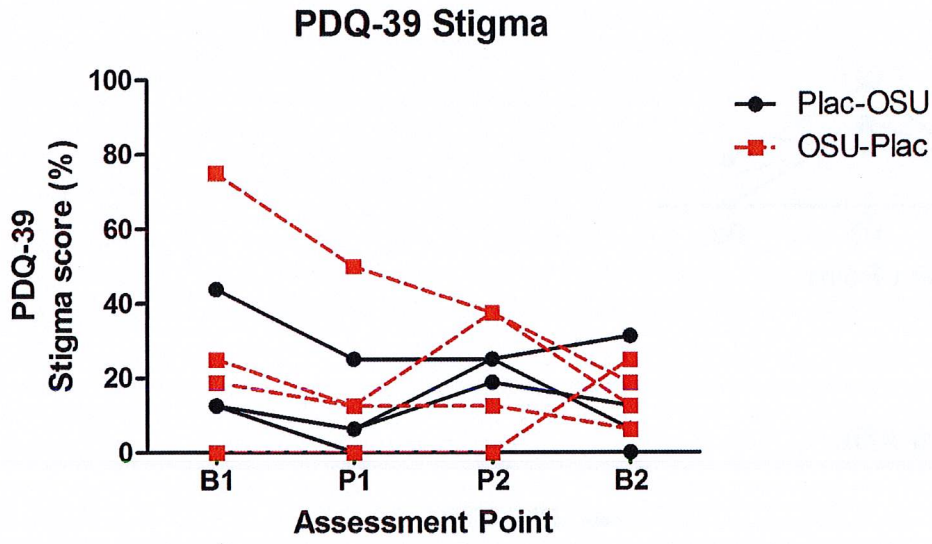


Figure 6e

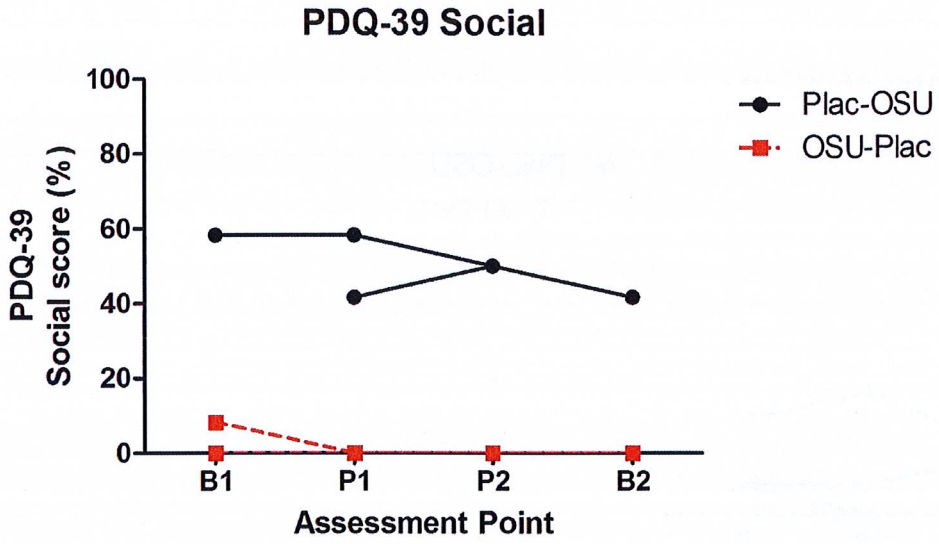


Figure 6f

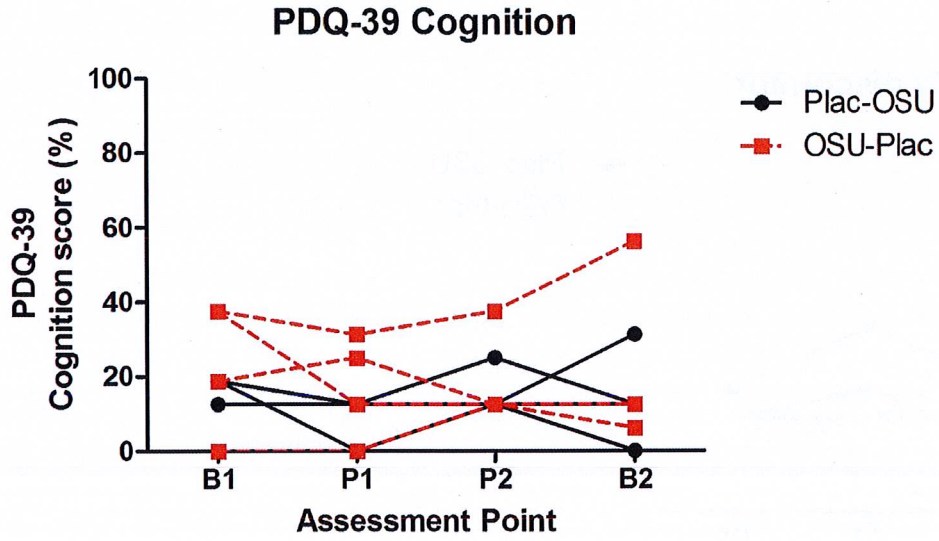


Figure 6g

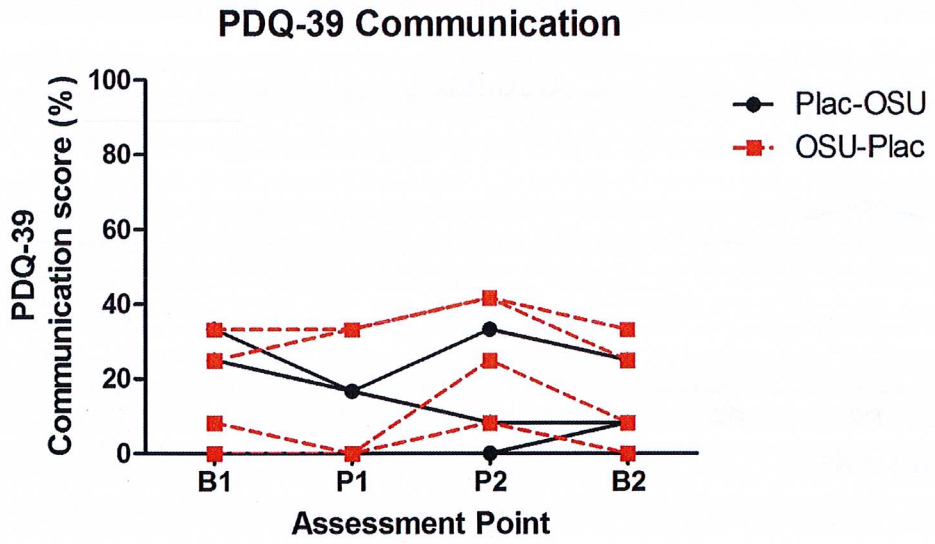
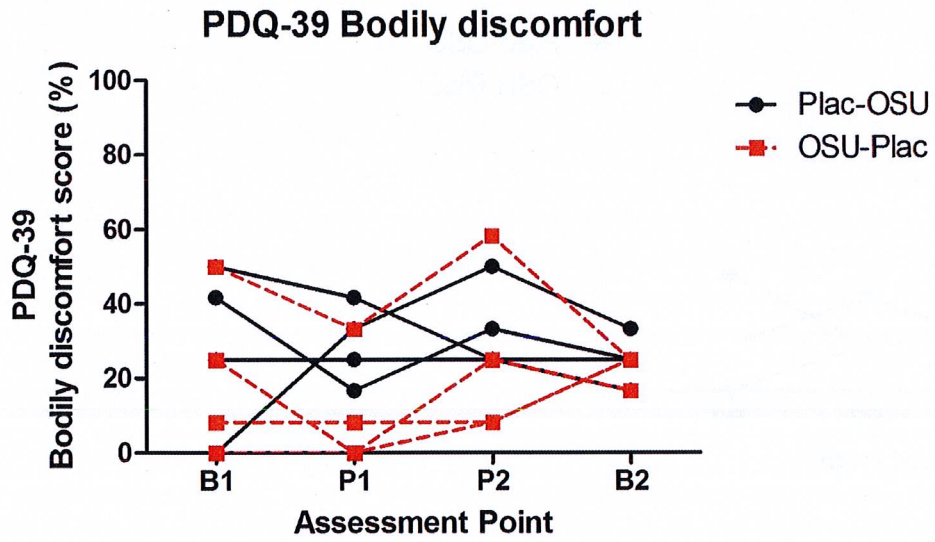


Figure 6h



In **Figure 7a-h** below, mean (with SEM - standard error of the mean) change in PDQ-39 score values between assessment points B1, P1 and P2 are shown for the treatment groups "osu-plac" (red curve) and "plac-osu" (black curve). Note that only assessment points P1 and P2 have been used for statistical testing of treatment effect.

Figure 7a

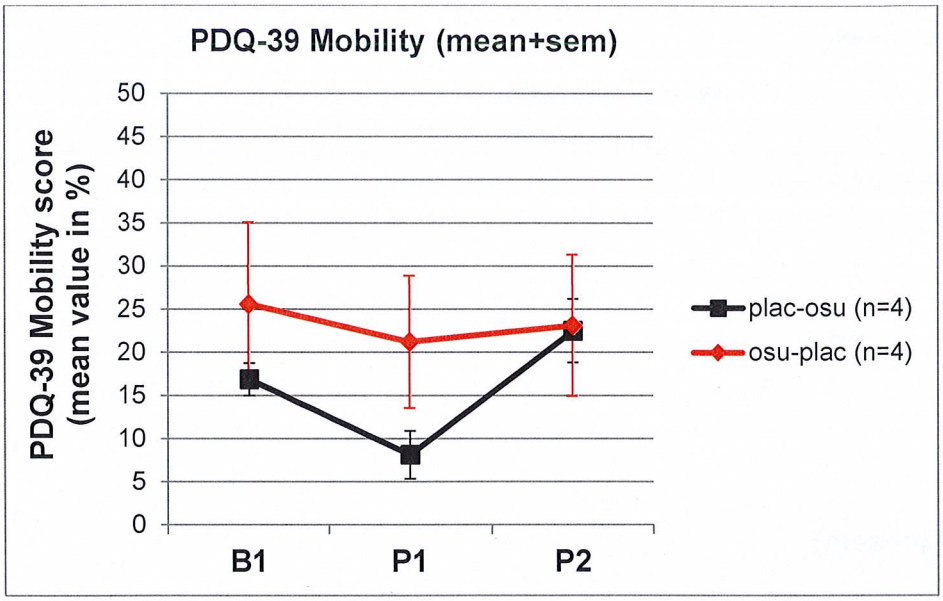


Figure 7b

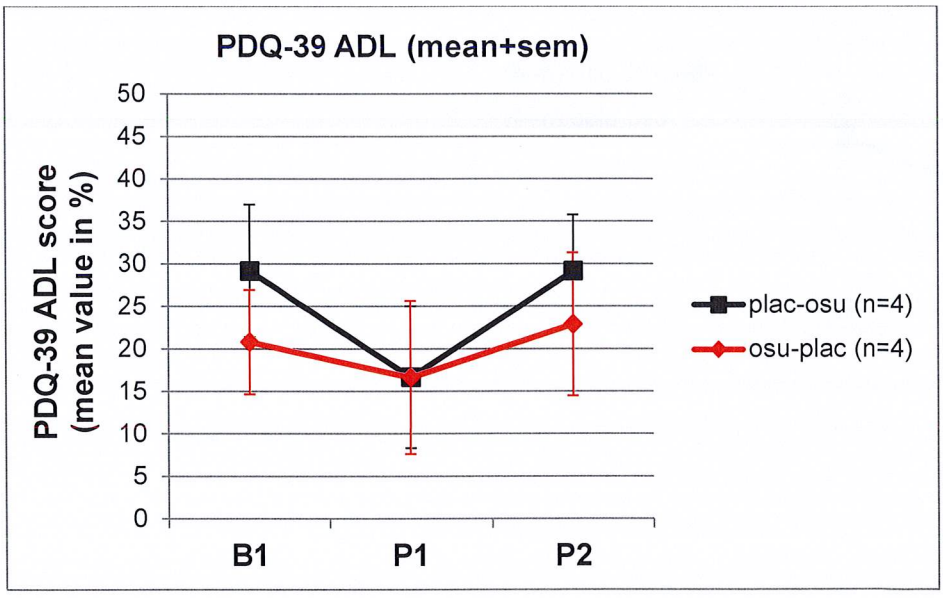


Figure 7c

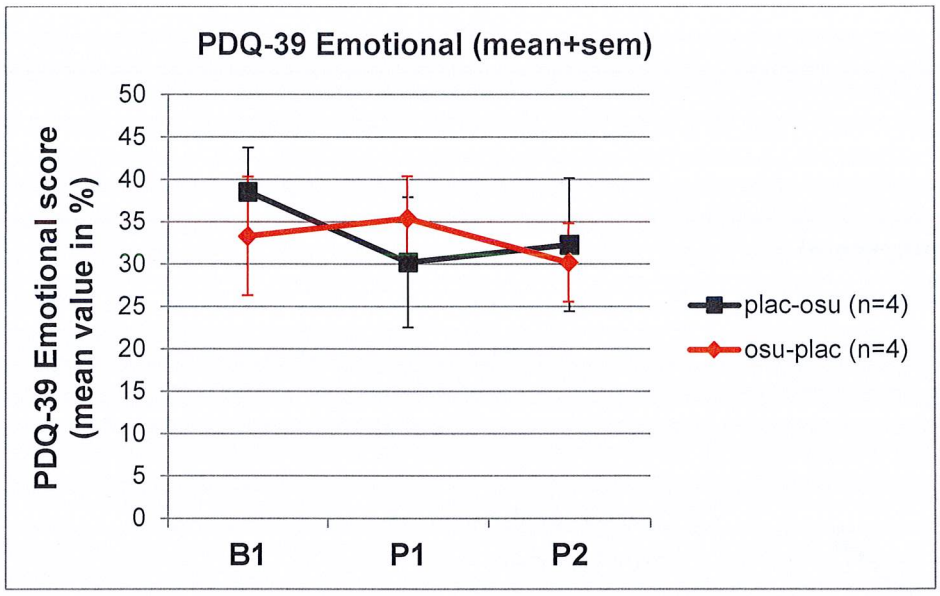


Figure 7d

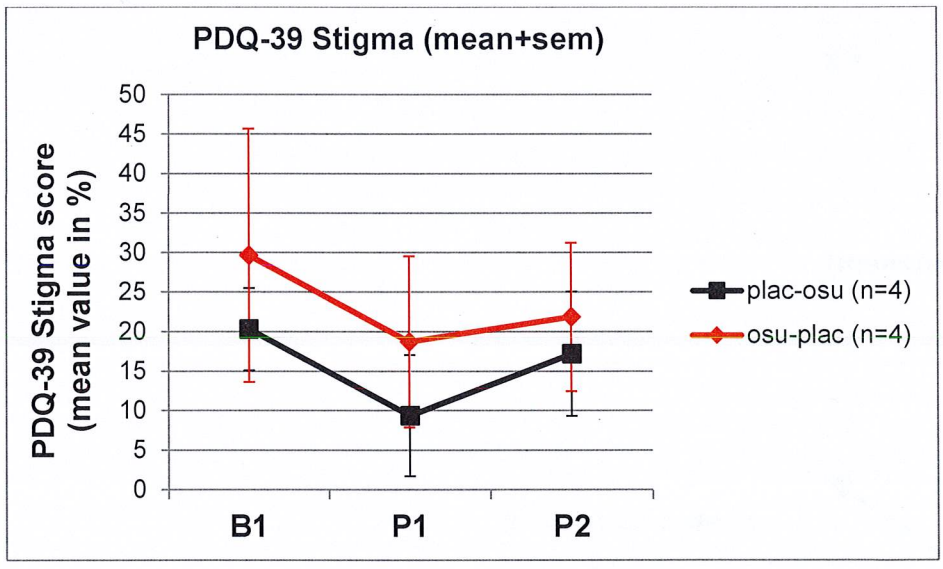


Figure 7e

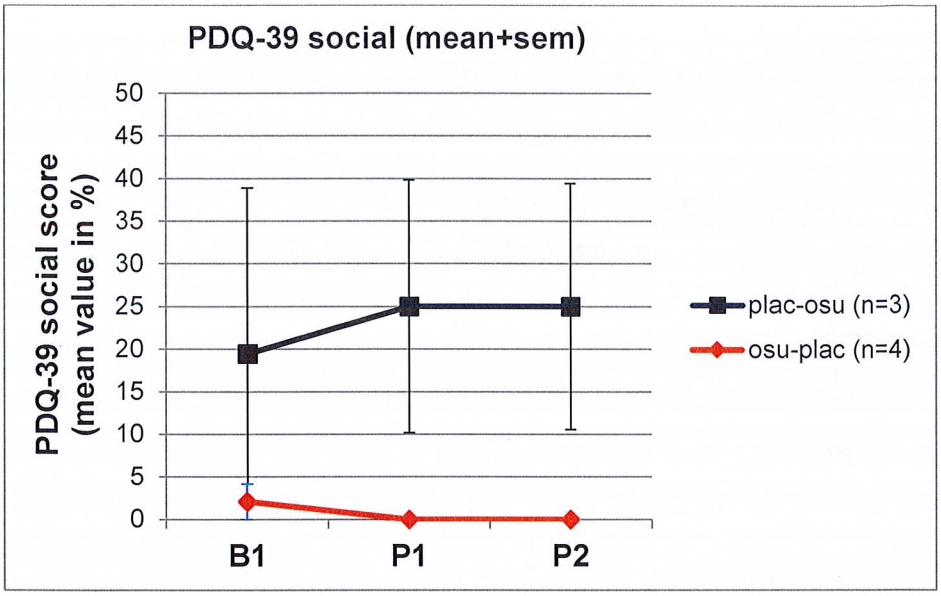


Figure 7f

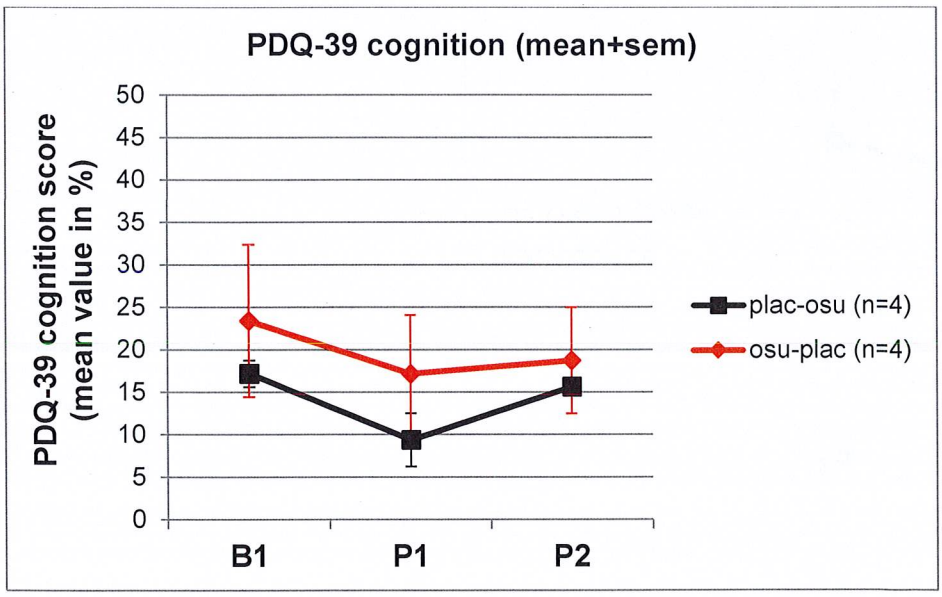


Figure 7g

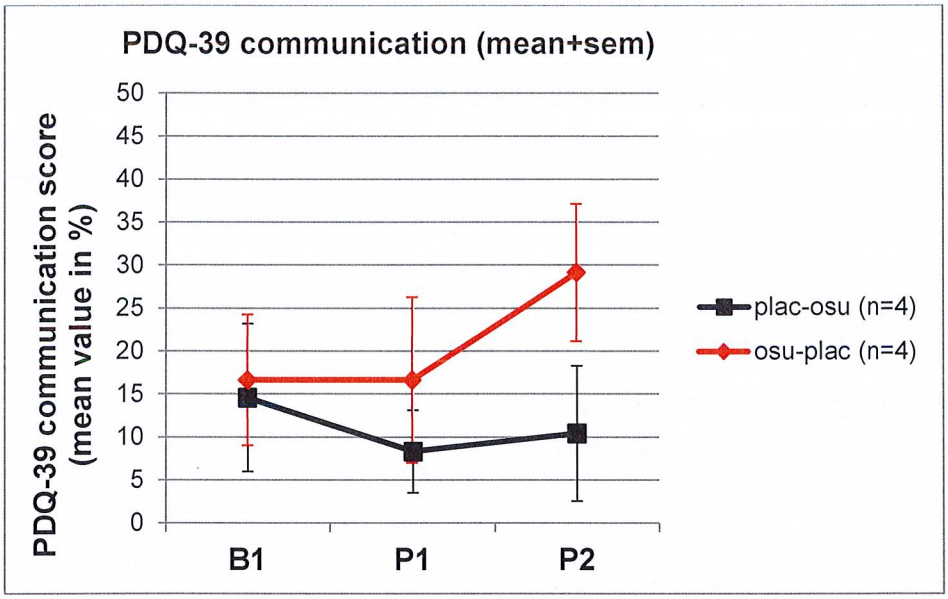
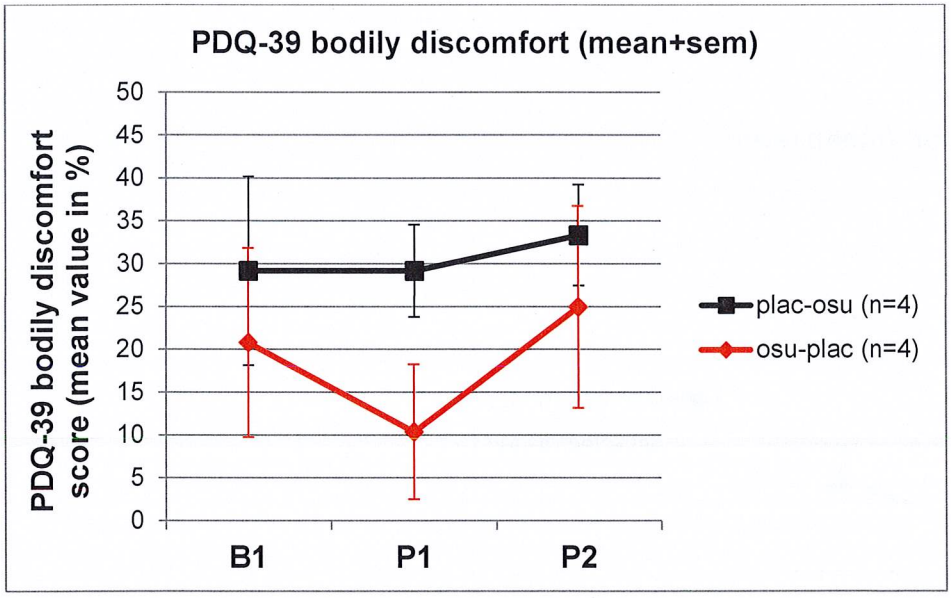


Figure 7h



BDI-II RESULTS

No statistically significant differences between intervention groups were found in BDI-II baseline data.

No statistically significant treatment effects were found for the Beck Depression Inventory II (BDI-II) scale. Individual BDI-II score values for the assessment points B1, P1, P2 and B2 are shown in **Figure 8a** below. Black curves represent patients in the group "plac-osu" and red curves patients in the group "osu-plac". Diagnostic cut-offs: 0-9: minimal depression; 10-18: mild depression; 19-29: moderate depression; 30-63: severe depression.

Figure 8a

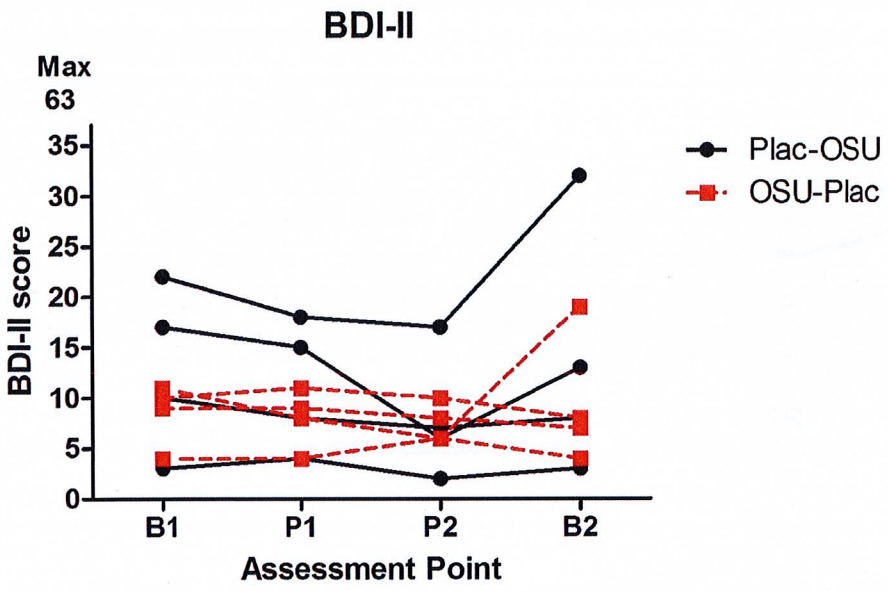
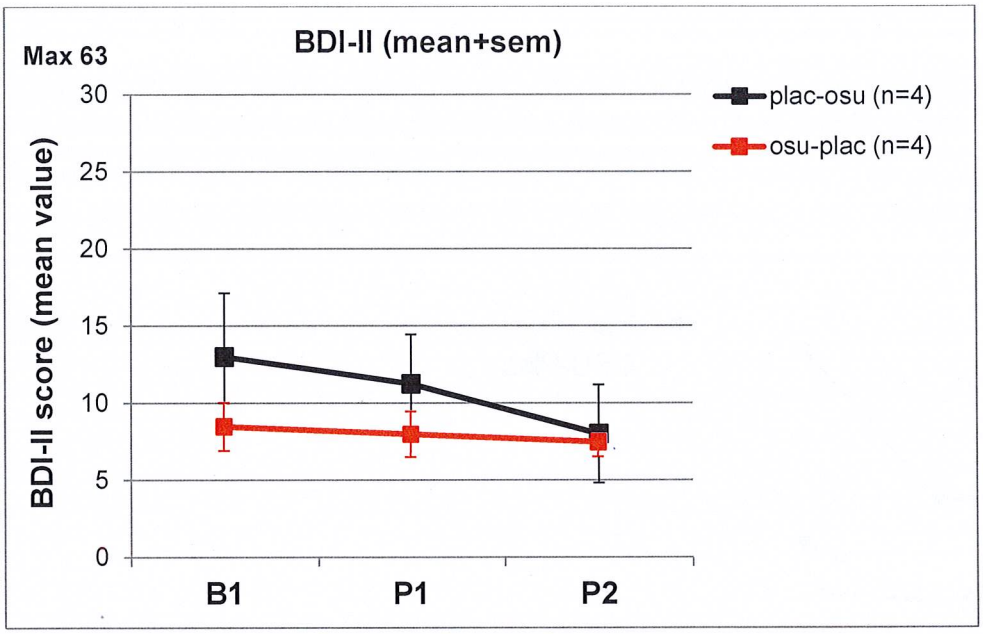


Figure 8b, shows the mean (with SEM - standard error of the mean) change in BDI-II score values between assessment points B1, P1 and P2 for the two treatment groups "osu-plac" (red curve) and "plac-osu" (black curve). Note that only assessment points P1 and P2 have been used for statistical testing of treatment effect.

Figure 8b



SAFETY EVALUATION

Data from all included patients that completed the study (8 patients), was used for the assessment of safety. In **Table 5** all safety variables are presented as descriptive data for the two treatment groups during treatment with (-)-OSU6162 and during treatment with placebo. ECG and laboratory tests are presented as number of patients with no abnormalities detected (NAD) or with abnormalities detected (AD). SBP, DBP and BMI are presented as group median with range. AE and SAE are presented as number of patients experiencing AE or SAE. Prolactin evaluation is presented separately in **Table 6**.

No clinically significant differences were found for baseline data concerning safety variables.

No clinically significant treatment effects were found in the laboratory safety variables, ECG, SBP, DBP or BMI. One patient in the plac-osu group had a pathological ECG in the form of VES (ventricular extrasystole) and QT-prolongation at follow up, 4 weeks after treatment with 90 mg/day of (-)-OSU6162 (see * Table 5).

Table 5. Safety evaluation. Shown is quantity (NO of patients) or median (range)

	Started with (-)-OSU6162		**Started with Placebo**	
Safety variable	**(-)-OSU6162 treatment**	**Placebo treatment**	**(-)-OSU6162 treatment**	**Placebo treatment**
ECG	4NAD/0AD	4NAD/0AD	3NAD/1AD*	4NAD/0AD
Laboratory tests #	4NAD/0AD	4NAD/0AD	4NAD/0AD	4NAD/0AD
SBP	122.5 (110-205)	120 (95-160)	137.5 (110-145)	125 (110-160)
DBP	70 (70-110)	75 (55-90)	80 (70-90)	80 (70-90)
BMI	23.3 (20.6-30.8)	23.2 (20.5-31.1)	21.2 (19-22.1)	21.5 (19.6-22.5)
AE+	4	1	4	0
SAE	0	0	0	0

*) One patient showed abnormalities in ECG at follow up in the form of VES and QT-prolongation.
#) Prolactin is reported separately see Table 6.
+) For description of AE see Table 7 and 8.
AD) Abnormalities Detected
NAD) No Abnormalities Detected

Prolactin concentration

Prolactin data is available from only 3 patients, due to technical problems with the analyses. All available data is shown in **Table 6**. This data shows an increase in prolactin concentration during (-)-OSU6162 treatment in all 3 patients studied. However, all values remained within normal limits.

Table 6. Change in Prolactin concentration

Patient	Treatment group	Baseline (B1)	OSU6162 treatment	Placebo treatment	Follow-up (B2)
6	osu-plac	3.61	9.21	8.58	6.30
7	osu-plac	1.71	2.37	1.88	1.80
8	plac-osu	1.97	2.60	1.75	Na

All values show Prolactin concentration in μg/L. Na = not analysed
Normal limits women: 4.8-23.4 μg/L (102-496 mIE/L)
Normal limits men: 4.1-15.3 μg/L (86-324 mIE/L)

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

No Serious Adverse Events (SAE) occurred during the study.

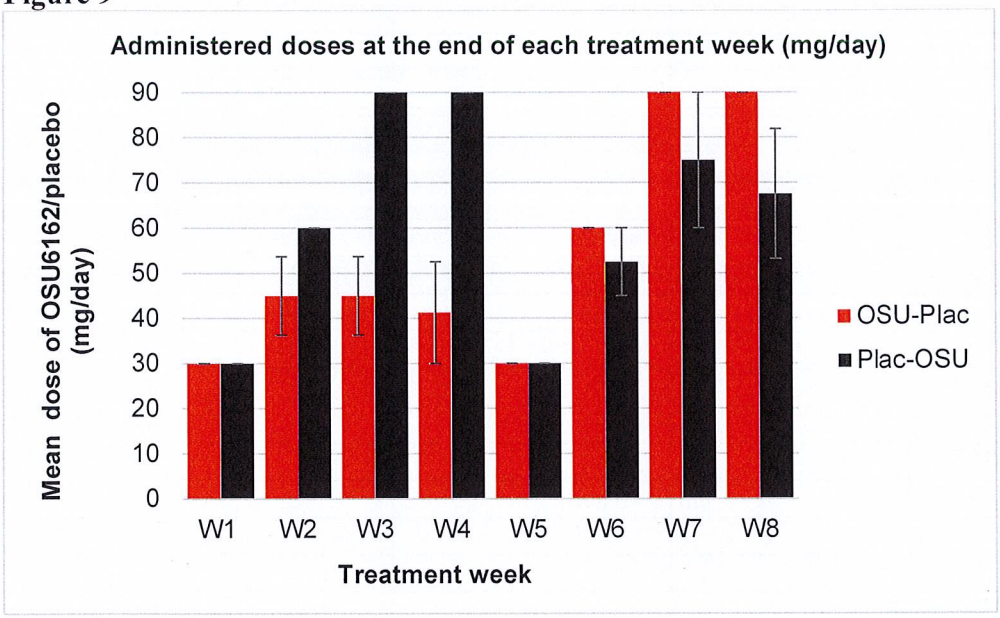
The number of experienced AE were significantly higher after (-)-OSU6162 treatment in both groups (p=0.0018; Mann-Whitney-U test). **Table 7** shows all AEs experienced by the patients during the study.

Table 7. Adverse Events experienced by the patients

Type of AE	During (-)-OSU6162 (n)	During Placebo (n)	At follow up (n)
PD motor symptoms			
Increased OFF	3		1
Increased rigidity	1		
Freezing	1		
PD overtreatment symptoms			
Hyperkinesia	1	1	
Increased dyskinesia	2		
PD non motor symptoms			
Ortostatism	1		
Somnolence	1		
Fatigue	2		
Other symptoms			
Palpitations	1		
Vertigo	2		
Nausea	1		
ECG abnormalities			
VES			1
QT-prolongation			1

Figure 9 below, shows the group mean (with SEM) doses of administered (-)-OSU6162 or placebo, at the end of each treatment week in the study. In this figure the dose limitations during (-)-OSU6162 treatment are clearly visible. Dose lowering during (-)-OSU6162 treatment was more frequent in the treatment group "OSU-plac".

Figure 9



In **Table 8** (below) individual dose adjustments and experienced AEs is shown. During (-)-OSU6162 treatment the study dose had to be reduced in 6 out of 8 patients (No: 1, 2, 5, 6, 7, 8), while a temporary dose reduction during placebo treatment was performed in 1 patient (No: 2). In three of these patients dose reduction was preceded by a medication stop for 1-3 days. In addition a 4 days medication stop was performed in one patient treated with 30 mg/day of (-)-OSU6162 because of increased rigidity (No: 4). However, the rigidity attenuated and the patient could continue according to plan. Another patient experienced increased OFF when treated with 30 mg/day of (-)-OSU6162 but decided to continue according to plan (No: 3). In three of the patients AEs were reduced or disappeared after dose reduction of (-)-OSU6162 (No: 1, 6, 7). However, in two patients the AE symptoms remained after dose reduction (No: 5 and 8). Persisting symptoms in patient 5 were increased dyskinesia and fatigue. Persisting symptoms in patient 8 were somnolence and nausea. Except for the reported somnolence and nausea in patient No 8, this patient also reported positive treatment effects during (-)-OSU6162 in the form of less hyperkinesia and better sleep. In patient No 1 a pathological ECG in the form of VES (ventricular extrasystole) and QT-prolongation was found at follow up, 4 weeks after treatment with 90 mg/day of (-)-OSU6162.

One patient (No 2) experienced severe hyperkinesia and freezing during treatment with 90 mg/day of (-)-OSU6162 leading to medication stop and dose reduction. These symptoms were somewhat less frequent after dose reduction (75 mg/day) but the hyperkinesia re-appeared during placebo treatment leading to a new medication stop. The hyperkinesia stayed unaltered while the patient continued according to plan. It is therefore uncertain if this AE was treatment related.

Three of the patients reported at follow up that they were in a better general health during the period corresponding to placebo treatment. One of them had more severe OFF-states and much more fluctuations between ON- and OFF-states during (-)-OSU6162 treatment.

Table 8: Individual dose adjustments including AEs

Treatment Group OSU-Plac	Dose of OSU6162 (mg/day) and AE				Dose of placebo (mg/day) and AE			
Week	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**
Patient 2	30	60	90 → 1 day medication stop→ 60 Hyper-kinesia; Freezing	75 Hyperkinesia and freezing less frequent	30 Hyperkinesia	30 → 3 days medication stop → 60 Hyperkinesia	90 Hyperkinesia	90 Hyperkinesia
Patient 5	30 Increased Dyskinesia Fatigue	30 Increased Dyskinesia Fatigue Ortostatism	30 Increased Dyskinesia Fatigue	30 Increased Dyskinesia Fatigue	30	60	90	90
Patient 6	30	60 → 30 Vertigo Palpitations Fatigue	30	30	30	60	90	90
Patient 7	30	60	90 → 60 Vertigo	30	30	60	90	90
Treatment Group Plac-OSU	Dose of placebo (mg/day) and AE				Dose of OSU6162 (mg/day) and AE			
Week	**W 1**	**W 2**	**W 3**	**W 4**	**W 5**	**W 6**	**W 7**	**W 8**
Patient 1	30	60	90	90	30	60	90 Increased OFF	60 Reduced OFF VES and QT-prolong-ation at Follow up
Patient 3	30	60	90	90	30 Increased OFF and Dyskinesia	60 Increased OFF	90 Increased OFF	90 Increased OFF
Patient 4	30	60	90	90	30 → 4 days medication Stop → 30 Increased rigidity	60	90	90
Patient 8	30	60	90	90	30 Increased OFF. Less hyperkinesia Better sleep	60 → 2 days medication stop → 30 Somnolence Nausea	30 Somnolence Nausea	30 Somnolence Nausea

DISCUSSION AND OVERALL CONCLUSIONS

In the present study, with the stepwise increasing dose level design and with the final dose of 45 mg twice daily, very mild non-serious side effects were expected. Due to its unique stabilizing properties we hypothesized that (-)-OSU6162 could alleviate symptoms caused by dopaminergic overstimulation, such as dyskinesia, but without causing deficits in dopaminergic function, and thus Parkinsonism. In this way, we expected (-)-OSU6162 to increase the time with satisfactory movement capacity without problematic dyskinesia and increase our patients' quality of life, which is the main goal of all treatment strategies in advanced PD. Instead the study was prematurely ended by the principal investigator because of dose limiting AEs. Actually, favourable effects of (-)-OSU6162 treatment were only present in one patient reporting alleviation of hyperkinesia and better sleep after dose 15 mg x 2. The positive effects disappeared at dose increase to 45 mg x 2 in the same patient, and a dose reduction back to 15 mg x 2 was necessary due to increased somnolence. In earlier studies patients with advanced Parkinson´s disease have been found to be very pharmacologically sensitive and need to be treated with much lower doses of (-)-OSU6162 compared to patients with other diagnoses or healthy volunteers (Report USA FDA IND 391A-CNS-0060-SR: Report of PD clinical study in US year 2000, not published; Tedroff 1998). This was also the case in this study since the study dose had to be reduced in 6 out of 8 patients, while a temporary dose reduction during placebo treatment was performed in 1 patient. The most frequent AE reported were increased OFF, fatigue, increased dyskinesia and vertigo, symptoms that may indicate both overtreatment and Parkinsonism

The low number of completed patients makes it´s hard to draw any reliable conclusions about the efficacy data. However, concerning safety there were no SAEs or drop outs present and most of the AEs seen were mild and dose dependent. Therefore, the study clearly concludes that (-)-OSU6162 doses may have to be titrated from very low levels in advanced PD patients.

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