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CLINICAL TRIAL PROTOCOL

TOLEDO

Multicenter, parallel-group, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of apomorphine subcutaneous infusion in Parkinson's disease patients with motor complications not well controlled on medical treatment

EudraCT-No.:	2013-000980-10
Protocol-No.:	CT-37527-13-0124
Date:	02 July 2014
Status:	Final 3.0 Including Amendment 2, 02 July 2014
Clinical Phase:	Phase III
Investigational Medicinal Product:	Apomorphine hydrochloride
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Table of Contents

List of Abbreviations

AE	Adverse Event
ALT	Alanine transaminase
AMS	Advanced Medical Services (CRO)
AR	Adverse Reaction
AST	Aspartate transaminase
BP	Blood Pressure
COMT	Catechol-O-methyltransferase
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DDCI	DOPA decarboxylase inhibitor
DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
ECG	Electrocardiography
EMA	European Medicines Agency
FPI	First Patient In
FU	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
IB	Investigator's Brochure
IC	Interim Contact
ICD	International Classification of Diseases
ICH	International Conference on Harmonization
ICH-GCP	Guidelines for Good Clinical Practice; CPMP/ICH/135/95, 17. January 1997
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intra-uterine Device
LDH	Lactate Dehydrogenase
L-dopa	L-3,4-dihydroxyphenylalanine
LOCF	Last Observation Carried Forward
LPI	Last Patient In
LPO	Last Patient Out
MAO	Monoamine Oxidase
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NIMP	Non-Investigational Medicinal Product
NMSS	Non-Motor Symptoms Scale
Pat. ID	Patient Identification Number
PD	Parkinson`s Disease
PDQ	Parkinson's Disease Quality of Life Questionnaire
PDSS	Parkinson's Disease Sleep Scale

PGIC	Patient`s Global Impression of Change
QUIP	Questionnaire for Impulsive-Compulsive Disorders in Parkinson`s Disease
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
UPDRS	Unified Parkinson's disease Rating Scale
V	Visit
WHO	World Health Organization

1 SYNOPSIS

Title	Multicenter, parallel-group, double-blind, placebo-controlled phase III study to evaluate the efficacy and safety of apomorphine subcutaneous infusion in Parkinson's disease patients with motor complications not well controlled on medical treatment
EudraCT No.	2013-000980-10
Protocol No.	CT-37527-13-0124
Version No. and Date	Final 3.0 / 02 July 2014
Clinical Phase	III
Trial Design	Randomized, multicenter, parallel-group, double-blind, placebo-controlled
Trial Indication	Parkinson's disease (PD) with insufficient control of motor fluctuations
Participating Countries	Multi-national in about 7 countries
Number of Trial Sites	Approximately 25 hospitals
Objective	The primary objective is to investigate the efficacy of apomorphine subcutaneous infusion compared to placebo in PD patients with motor fluctuations not well controlled on medical treatment. The secondary objective is to investigate the safety and tolerability of apomorphine subcutaneous infusion therapy.
Number of Patients	Planned number of patients randomized: A total of 102 patients.
Investigational Medicinal Product (IMP)	Apomorphine hydrochloride 5 mg/ml solution for infusion in pre-filled syringe
Dose and Route of Administration	Subcutaneous continuous infusion during waking period. The hourly flow rate is adjusted during Visit 3 and during the first 4 weeks of treatment, to doses of 3 mg/hour up to 8 mg/hour, depending on individual tolerability and efficacy. The target dose is each patient´s individual optimized dose or the maximum dose of 8 mg/hour. The targeted delivery cycle should be 16 hours with individual variations of +/- 2 hours allowed.
Application Scheme	The starting dose for apomorphine subcutaneous infusion will be 1 mg/hour during the first day of infusion. If no adverse effects occur, the hourly flow rate will then be increased in the following manner:

	• by 0.5 to 1 mg/hour each day, until the end of Visit 3 or until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first. • At the weekly visits up to week 4 (V6): by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated hourly dose has been reached, whichever occurs first
Control Group	Placebo: saline infusion, administered by the same pump system as apomorphine.
Trial Duration per Patient	The overall trial duration for each patient can be up to 16 months including screening phase, 3 months randomized treatment + 12 months open-label treatment.
Planned Trial Period	Planned recruitment duration: 12 months 1st quarter 2014 (FPI = First Patient In) to 2nd quarter 2016 (LPO = Last Patient Out Follow-up)
Inclusion Criteria	• Male or female patients aged ≥30 • Diagnosis of idiopathic Parkinson's disease of >3 years' duration, defined by the UK Brain Bank criteria (with the exception of >1 affected relative being allowed), without any other known or suspected cause of Parkinsonism • Hoehn & Yahr stage up to 3 in the ON and 2 to 5 in the OFF state • Motor fluctuations not adequately controlled on medical treatment including L-dopa which was judged to be optimal by the treating physician • Average of OFF time>= 3 h/day based on screening and baseline diary entries with no day with < 2 hours of OFF time recorded • Stable medication regimen, with a stable dose of L-dopa administered in at least 4 intakes, for at least 28 days prior to baseline. All oral or transdermal antiparkinsonian drugs are permitted, with the exception of budipine. This regimen may include the use of L-dopa /DDCI rescue medication if this occurs up to 2 times a day, at doses of up to 200 mg L-dopa/day • Patients must be able to differentiate between the ON and OFF state and between troublesome and non-troublesome dyskinesias • Male and female patients must be compliant with a highly effective contraceptive method (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method) during the study and for 12 months open-label phase, if sexually active • Females of childbearing potential must have a negative serum hCG or urine pregnancy test at screening

	• Ability to accurately complete a paper diary on designated days (with assistance from caregivers, if required), recording periods when they are "ON without troublesome dyskinesia", "ON with troublesome dyskinesia", OFF, and sleeping • Written informed consent prior to enrolment, after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the study treatments • Patients considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator
Exclusion Criteria	• History of respiratory depression • Hypersensitivity to apomorphine or any excipients of the medicinal product • High suspicion of other parkinsonian syndromes • Presence of severe freezing or clinically relevant postural instability leading to falls during the ON state • Concomitant therapy or within 28 days prior to baseline with: apomorphine pen injections, alpha-methyl dopa, metoclopramide, reserpine, neuroleptics, methylphenidate, or amphetamine; intrajejunal L-dopa • Previous use of apomorphine pump treatment • History of deep brain stimulation or lesional surgery for PD • Any medical condition that is likely to interfere with an adequate participation in the study, including e.g. current diagnosis of unstable epilepsy; clinically relevant cardiac dysfunction and/or myocardial infarction or stroke within the last 12 months • Symptomatic, clinically relevant and medically uncontrolled orthostatic hypotension • Patients with a borderline QT interval corrected for heart rate according to Bazett's formula (QTc) of >450 ms for male and >470 ms for female at Screening or history of long QT syndrome; or >450 ms absolute duration • Clinically relevant hepatic dysfunction (total bilirubin >2.0 mg/dL, ALT and AST >2 times the upper limit of normal) • Clinically relevant renal dysfunction (serum creatinine >2.0 mg/dL); • Pregnant and breastfeeding women • Clinically relevant cognitive decline, defined as MMSE ≤24 or according to DSM IV criteria for dementia • Active psychosis or history of at least moderate psychosis in the past

	year, or with medically uncontrolled severe depression; very mild illusions or hallucinations in the sense of "feelings of passage or presence" with fully retained insight are not an exclusion criterion • Known history of melanoma • Any investigational therapy in the 4 weeks prior to randomization • History or current drug or alcohol abuse or dependencies
Randomization Criteria	Patients who are eligible according to the in-/exclusion criteria will be randomized to treatment with either apomorphine or placebo (physiological saline) infusion.
Primary Endpoint	Primary efficacy variable is the absolute change in time spent "OFF" from baseline to the end of 12 weeks double-blind treatment period based on patient diaries
Secondary Endpoints	• Percentage of patients with response to therapy, defined as an OFF time reduction of at least 2 hours, from baseline to end of 12 weeks double-blind treatment period • Patient Global Impression of Change • Absolute Change in time spent "ON without troublesome dyskinesia" • Change in oral L-dopa and L-dopa equivalent dose • Change in Unified Parkinson's Disease Rating Scale (UPDRS Part III motor examination) during ON periods • Change in Quality of Life (using PDQ-8)
Exploratory Endpoints	• Change in Score of the Non-Motor Symptoms Scale for PD; • Change in MDS-UPDRS Part I patient questionnaire = non-motor experiences of daily living • Change in MDS-UPDRS II, assessed separately for ON and OFF states • Change in MDS-UPDRS Part IV fluctuations = items 4.3 and 4.4 combined • Drop-outs due to lack of efficacy • Beck Depression Scale • PDSS (PD Sleep Scale)
Safety Endpoints	• Evaluation of adverse events and local tolerability • Skin changes • Full blood count • Epworth Sleepiness Scale • QUIP • C-SSRS (Columbia Suicide Severity Rating Scale)

Procedures (Summary)	Each site has access to an internet based eCRF in order to document the treatment of patients online. Patients will be trained in completion of paper based diaries during Screening visits 1 and 2. At Screening and at Baseline, the measurements and examinations as listed in the Trial Schedule (e.g. ECG, Laboratory, UPDRS, Non motor scale, QoL, etc.) will be performed. Patients will be admitted to hospital on the day of the Baseline visit continuing their regular medical treatment. In those centers where the established standard practice for apomorphine titration is as an out-patient, Visit 3 may be conducted as day-case hospitalization for a minimum of 8 hours daily. Antiemetic premedication will be administered according to local standards. Recommended pre-treatment use of domperidone is 10 mg tid starting 3 days prior to the infusion. The Visit 3 is scheduled to be 5 days and can be extended up to 10 days if necessary. On the day following Baseline patients will take their regular medication and the pump will be initiated. Prior to the study start and throughout Visit 3, the patients and/or carers will be trained in the use of the apomorphine infusion system by the study personnel. A minimum of 2 investigators are required at each site. If this is absolutely necessary for logistical and staffing reasons, Investigator 2 does not need to be a physician but may be a trained study nurse with experience and training in the performance of the relevant scales, including UPDRS. Investigator 1 is in charge of the following: • making dose changes based on efficacy and adverse events, • reviewing the patient diaries, • taking the history from patients and/or carers on efficacy, • assessing tolerability and safety, including checking the state of the abdominal skin and recommending related treatments and including the formal safety assessments (review of all safety questionnaires), • responding to any laboratory changes. Investigator 2 performs all other assessments of efficacy (UPDRS, PGIC). To maintain the blinding patients and carers are advised at the beginning of each study visit not to discuss any local or other adverse reactions to the infusion with Investigator 2. Investigator 2 will not review any lab results. During the open-label phase either Investigator may perform all assessments During the double blind treatment period (V3 to V10) 8 visits are planned. All concomitant medication and apomorphine should be maintained stable after Visit 6 and may only be adjusted if clinically necessary due to lack of effect or adverse events.

Statistical Analysis	The primary endpoint of this study is the absolute change in OFF-time from baseline to end of double-blind treatment. A Wilcoxon Rank Sum Test will be used to test the primary hypothesis (superiority of apomorphine vs. placebo). The test shall be performed using a Type I error level of 0.05 two-sided and 80% power. Based on previous experience / review of published apomorphine data it is assumed that an OFF-time baseline value of 6.5 hours will be reduced to 3.5 hours under apomorphine and to 5 hours under Placebo. A two-sample t-Test allowing for unequal variances (Standard deviation of 1.75 hours for apomorphine and 2.5 hours for placebo) requires 68 evaluable patients (1:1 treatment balance). Allowing 5% extra for the non-parametric testing 72 evaluable patients are needed. If 30% of the randomized patients are not evaluable for the primary endpoint, a total of 102 patients need to be randomized.

TRIAL SCHEDULE

Trial Phase	**Screening**		**Base-line**	**Double-Blinded Treatment Period**						
Visits	**V1**	**V2[m]**	**V3**		**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Target Date	**Screening 1 up to -21d**	**Screening 2 up to -14d**	**Day 0**	**Day 4 + 5 days[a]**	**Day 14 +/- 3 days**	**Day 21 +/- 3 days**	**Day 28 +/-3 days**	**Day 42 +/- 3 days**	**Day 56 +/-3 days**	**Day 70 +/-3 days**	**Day 84 +/-3 days**
Week			**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 End of Blinded Treatment[b]**
			In/Out-patient stay								
			Dose adjustment								
Informed consent	●[e]										
Medical history	●										
Physical Examination	●[g]		●	●[d]	●	●	●	●	●	●	●
Vital Signs[o]	●		●[n]	●[d]	●	●	●	●	●	●	●
Clinical Chemistry	●		●				●		●		●
Hematology	●		●				●		●		●
ECG	●		●	●[d]	●			●			●
Pregnancy test*	●[l]										
Inclusion/ exclusion criteria	●		●								
Quality of Life (PDQ-8)			●					●			●
Diary documentation	●[k]	●[k]	●	●[d]	●	●	●	●			●
MDS-UPDRS			●					●			●
PGIC			●					●			●
Non-Motor Symptoms Scale			●					●			●
Beck			●					●			●
QUIP			●					●			●
Epworth Sleepiness Scale			●					●			●
PDSS			●					●			●
C-SSRS			●					●			●
Randomization			●								
Training on the infusion system				●	●[l]	●[l]	●[l]	●[l]	●[l]	●[l]	

Trial Phase	**Screening**		**Base-line**	**Double-Blinded Treatment Period**						
Visits	**V1**	**V2[m]**	**V3**		**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Target Date	**Screening 1 up to -21d**	**Screening 2 up to -14d**	**Day 0**	**Day 4 + 5 days[a]**	**Day 14 +/- 3 days**	**Day 21 +/- 3 days**	**Day 28 +/-3 days**	**Day 42 +/- 3 days**	**Day 56 +/-3 days**	**Day 70 +/-3 days**	**Day 84 +/-3 days**
Week			**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12 End of Blinded Treatment[b]**
			In/Out-patient stay								
			Dose adjustment								
Handout of IMP to the patients				●[d]	●	●	●	●	●	●	
Return of unused IMP					●	●	●	●	●	●	●
Dose changes of IMP			●	●[d]	●	●	●	●	●	●	●
Changes in concomitant diseases and medication	●[f]		●	●[d]	●	●	●	●	●	●	●
Documentation of adverse events		●	●	●[d]	●	●	●	●	●	●	●
Assessment of local and general tolerability				●[d]	●	●	●	●	●	●	●

* as often as needed according to local requirements

a. Minimum of 4 days on treatment - Maximum of 10 days
b. Assessments to be performed in case of earlier termination of the blinded treatment
c. Assessments to be performed in case of earlier termination of the study
d. Assessments to be performed at discharge
e. Written informed consent must be obtained prior to any study-related procedures or evaluations
f. Documentation of all medications taken within 30 days prior to first dose of study therapy
g. Height and weight measurements to be performed at screening only
h. Within 1-3 days after End of Blinded Treatment Visit
i. Urine pregnancy test is acceptable
j. Duration defined by the investigator according to local treatment standards
k. Diary training
l. If required
m. An optional screening visit might be necessary, if patient does not complete diary correctly prior to V2
n. Orthostatic BP to be taken 75 to 90 minutes after each dose increase. Triplicate supine BP (after 5 minutes rest) followed by standing BP (within 1 – 3 minutes of standing)
o. V4 to V15: Single supine and standing readings of orthostatic BP measurements will be taken at the clinic, after start of infusion.

Trial Phase	**Dose adjustment**[l]	**Open Label Treatment Period**[n]							
Visits	**V11**	**V11a** ☎	**V12**	**V12a** ☎	**V13**	**V13a** ☎	**V14**	**V14a** ☎	**V15 End of Study**[c]
Target date	**V10 + 1 to 3 days**		**V11 + 84 days**		**V11 + 168 days**		**V11 + 252 days**		**V11 + 365 days**
Week (calculated from V11)	**Week 0**	**Week 6 ± 1 week**	**Week 12 ± 2 weeks**	**Week 18 ± 1 week**	**Week 24 ± 2 weeks**	**Week 30 ± 1 week**	**Week 36 ± 2 weeks**	**Week 44 ± 1 week**	**Week 52 + 2 weeks**
Informed consent	●[e]								
Physical Examination			●		●		●		●
Vital Signs[o]	●		●		●		●		●
Clinical Chemistry			●		●		●		●
Hematology			●		●		●		●
ECG			●		●		●		●
Pregnancy test (as required)									
Quality of Life (PDQ-8)			●		●		●		●
Diary documentation			●		●		●		●
MDS-UPDRS			●		●		●		●
PGIC			●		●		●		●
Non-Motor Symptoms Scale			●						●
Beck			●						●
QUIP			●						●
Epworth Sleepiness Scale			●						●
PDSS			●						●
C-SSRS			●		●		●		●
Training on the infusion system	●[l]		●[l]		●[l]		●[l]		
Handout of IMP to the patients	●		●		●		●		
Return of unused IMP			●		●		●		●
Dose changes of IMP	●		●		●		●		●
Changes in concomitant diseases and medication	●	●	●	●	●	●	●	●	●
Documentation of adverse events	●	●	●	●	●	●	●	●	●
Assessment of local and general tolerability	●		●		●		●		●

2 INTRODUCTION AND RATIONALE

2.1 Indication

Parkinson`s Disease (PD) is one of the most frequent neurodegenerative disorders. 100-200/100.000 people are affected by PD in Germany. Prevalence increases with age; in the German population >65 years, the prevalence is elevated to 1.800/100.000 (Eggert et al., 2012). Across Europe, prevalence estimates range between 108 and 257/100.000 (von Campenhausen et al., 2005). PD affects both sexes approximately equally.

Patients with PD suffer from muscle rigidity, resting tremor, postural instability and bradykinesia or akinesia. Flexed posture and freezing (motor blocks) have also been included among the classical features of parkinsonism (Jankovic, 2008). Primarily, the motor symptoms of PD result from the death of dopaminergic neurons in the substantia nigra, leading to striatal dopamine deficiency (Dauer und Przedborski, 2003). The neurotransmitter dopamine modulates post-synaptic signaling in the striatum, influencing motor behavior.

Oral administration of the dopamine precursor levodopa (L-3, 4-dihydroxyphenylalanine, L-dopa) reduces the classical motor symptoms. L-dopa is converted to dopamine in the presynaptic dopaminergic nerve endings (Ribaric, 2012). The replacement therapy with L-dopa restores terminal dopamine levels in the striatum. The antiparkinsonian effect is mediated by the stimulation of postsynaptic D2 receptors (Ribaric, 2012). After significant initial improvement, the progression of PD is often accompanied by a progressive shortening of the clinical response to L-dopa. These fluctuations in motor function have been termed ON/OFF fluctuations. Progressive degeneration of the dopaminergic transmission results in a reduced capacity of taking up exogenously administered L-dopa and its conversion to dopamine for storage and release (Chase et al., 1993; Varanese et al., 2011). Erratic gastrointestinal absorption may contribute to the clinical problem of unpredictable motor response or failure of individual doses of L-dopa to induce an ON phase. Complex postsynaptic changes in the striatal expression of neuropeptides and in firing patterns are thought to underlie the formation of dyskinesias, or involuntary movements, which occurs in many of the patients with advanced PD (Obeso et al., 2000).

Motor fluctuations and dyskinesia develop in 50% of patients after 5 years and in 80% of patients after 10 years of L-dopa treatment (Chase et al., 1993; Schrag und Quinn, 2000). Advanced and end-stage PD patients experience an enhanced sensitivity to small changes in plasma L-dopa levels (Lang und Lozano, 1998; Varanese et al., 2011). The transition from good motor (ON state) to poor motor (OFF state) function occurs when brain L-dopa falls below the threshold needed to adequately stimulate striatal dopamine receptors (Dewey et al., 2001). The reduction in the dose of L-dopa often improves dyskinesias, but increases the duration and severity of the OFF periods (Deleu et al., 2004).

2.2 Test compound and rationale

The dopamine agonist apomorphine has shown good effect on the ON-OFF phenomenon. Apomorphine directly stimulates the striatal presynaptic and postsynaptic dopamine D1 and D2 receptors (Ribaric, 2012). In contrast to L-dopa, apomorphine is not concentrated and converted in the presynaptic dopaminergic endings. Its motor effects are therefore not dependent on the presence of functional presynaptic nerve endings (Ribaric, 2012).

Two principle approaches are applied for the treatment of patients with fluctuating PD: intermittent subcutaneous “rescue” injections of apomorphine and continuous diurnal subcutaneous apomorphine infusions (Poewe und Wenning, 2000). Intermittent subcutaneous injections produce antiparkinsonian benefit comparable to L-dopa and the efficacy of apomorphine injections has been demonstrated in placebo-controlled, randomized studies, both as single doses and in a longer-term (4 weeks) study, which showed that 95% of OFF periods could be terminated using apomorphine, compared with 23% on placebo (Dewey et al., 2001).

Continuous subcutaneous apomorphine infusion has been shown to be a highly effective treatment in patients with motor fluctuations in several studies, some of which were long-term (up to 5 years of follow-up). Level 1 evidence from randomized studies, however, is still lacking (Fox et al., 2011).

Clinical practice has shown that, for PD patients with severe motor fluctuations who are poorly controlled by conventional treatment, continuous apomorphine infusion can be an effective and well-tolerated option. It has been noted that this nonaggressive technique is easy to perform and relatively easy to control (Garcia Ruiz et al., 2008).

2.2.1 Summary of Preclinical Data

Repeat dose subcutaneous toxicity studies revealed no special hazard for humans, beyond the information included in the SmPC.

In vitro genotoxicity studies demonstrated mutagenic and clastogenic effects, most likely due to products formed by autoxidation of apomorphine. However, apomorphine was not genotoxic in the in vivo studies performed. The effect of apomorphine on reproduction has been investigated in rats. Apomorphine was not teratogenic in this species, but it was noted that doses which are toxic to the mother can cause loss of maternal care and failure to breathe in the newborn. No carcinogenicity studies have been performed.

2.2.2 Summary of Previous Clinical Trials

2.2.2.1 Efficacy Data

Compared to baseline, several studies showed a significant reduction of levodopa dosage or levodopa equivalent dose in patients on continuous apomorphine pump therapy. Daily OFF time has been shown to be reduced by up to 80% in multi-center studies (Manson et al., 2002; Di Rosa et al., 2003; De Gaspari et al., 2006; Garcia Ruiz et al., 2008; Sixel-Döring et al., 2011). No noticeable difference in the daily OFF-time reduction was found comparing patient groups receiving 24-hours infusion to groups receiving waking-day hours infusions (Deleu et al., 2004) although this approach can be used successfully in some patients with severe nocturnal OFFs (Manson et al., 2002). Continuous subcutaneous apomorphine infusion has been shown to be a safe and effective treatment for patients for whom subthalamic nucleus deep brain stimulation is contraindicated (Drapier et al., 2012).

In a non-randomized study, apomorphine pump treatment led to significant improvements compared to baseline in a number of non-motor symptoms, including the total Non Motor Symptom Scale and in quality of life, in contrast to a control group of eligible patients who had not received funding for the treatment (Martinez-Martin et al., 2011).

Several studies have also highlighted a possible effect on dyskinesias in patients with motor complications. In several uncontrolled studies, dyskinesias have been shown to improve by up to 58% from baseline, although this effect was not observed by all investigators. It has been suggested that it might be the marked reduction or discontinuation of oral medication that can be achieved in some patients that may underlie the observed dyskinesia improvement in those studies (Katzenschlager et al., 2005; Garcia Ruiz et al., 2008) (Manson et al., 2002; Morgante et al., 2004).

In a prospective, open clinical trial Katzenschlager et al., 2005 described a reduction of OFF time by about 1.3 h after 3 months with an increasing effect after 6 months to -38% (-2.4h/d) at apomorphine infusion using doses of 57.8 mg/d (3 months) and 75.2 mg/d (6 months) with a concomitant reduction of L-DOPA (mg/d) by -58% after 6 months (Katzenschlager et al., 2005).

Table 1 Subjective measures of dyskinesias and parkinsonism and dosages of L-dopa, L-dopa equivalent unit, and apomorphine months (Katzenschlager et al., 2005).

	Baseline	3 mo.	6 mo.	Change baseline–6 mo.	*P*, difference (6 mo. vs. baseline)
Off hours/day	6.3 (2.7)	5.0 (2.8)	3.9 (2.1)	−38% = 2.4 hours	<0.05
On-time duration (% of waking day)	66.2 (13.1)	73.2 (16.1)	79.1 (10.0)	+20%	<0.01
UPDRS 32 (dyskinesia duration)	2.1 (0.8)	1.7 (1.0)	1.3 (0.7)	−40%	<0.01
UPDRS 33 (dyskinesia severity)	2.4 (1.1)	1.5 (1.0)	1.7 (0.8)	−31%	<0.05
Lang and Fahn scale (ADL)	15.1 (3.6)	13.8 (5.2)	12.0 (3.4)	−21%	<0.05
Severity + duration in diaries (cm on VAS)	39.0 (25.5)	22.7 (18.7)	16.1 (9.4)	−58%	<0.01
L-Dopa (mg/day)	1629 (750–3700)	892 (100–1850)	735 (100–1850)	−55%	<0.01
LEU (mg/day)	1867 (900–3834)	965 (125–2195)	794 (125–1884)	−58%	<0.01
Apomorphine, as infusion (mg/day)	–	57.8 (31.5–91.0)	75.2 (45.0–127.5)	–	–

Data are expressed as mean (SD), except dosages, which are expressed as mean (range).
UPDRS, Unified Parkinson's Disease Rating Scale; ADL, activities of daily living; VAS, visual analogue scale; LEU, L-dopa equivalent unit (see Patients and Methods section).

2.2.2.2 Safety Data

Safety data are summarized in the regular PSUR in the latest version (2008), and are in accordance with the labeled safety information.

Possible adverse effects of apomorphine infusion therapy include an increase in dopaminergic effects such as nausea, orthostatic hypotension, or ankle edema. Dyskinesias may worsen, particularly during the initial phase while oral treatment has not been reduced (despite the fact that medium - to long-term dyskinesia reduction has been observed in many patients). Somnolence has been described. Unplanned episodes of sleep during daytime have occurred on all dopamine agonists and this implies a risk when driving a car.

Hemolytic anemia is a rare adverse effect and is not specific to apomorphine as it has been observed on L-dopa as well. Regular checks of full blood count are usually recommended although the optimum intervals have not been universally established (Stibe et al., 1988; Manson et al., 2002; Katzenschlager et al., 2005; Garcia Ruiz et al., 2008).

Neuropsychiatric adverse effects may occur on any parkinsonian drug. In particular, dopamine agonists have been associated with the occurrence of impulse control disorders, such as pathological gambling, hypersexuality and compulsive buying or eating (Weintraub et al., 2010). All patients initiated on any dopamine agonist must be informed of this possible side effect, which has been observed in 13.4% of PD patients in a large survey (Weintraub et al., 2010). This survey did not include patients on apomorphine but clinical observations strongly suggest that the risk of impulse control disorders exists on apomorphine as well.

There is limited data on other potential neuropsychiatric adverse effects. Hallucinations and confusion may occur but there is some evidence suggesting that this may be less

pronounced than with oral dopamine agonists and improvement in existing hallucinations has also been observed (van Laar et al., 2010).

2.3 Rationale for the Planned Trial

Despite the wide and increasing use of apomorphine subcutaneous infusion, mainly as replacement of multiple injections, level one evidence from a randomized placebo-controlled trial in apomorphine infusion naïve PD patients with motor fluctuations not well controlled on medical treatment is currently lacking. The planned trial is intended to investigate the efficacy and safety of apomorphine infusion in this clinical setting to provide such evidence under randomized and controlled conditions.

3 OBJECTIVES AND ENDPOINTS OF THE TRIAL

3.1 Objectives

The primary objective of the trial is to investigate the efficacy of apomorphine subcutaneous infusion compared to placebo in PD patients with motor fluctuations not well controlled on medical treatment. The secondary objective is to investigate the safety and tolerability of apomorphine subcutaneous infusion therapy.

3.2 Primary Endpoint

Primary efficacy variable is the absolute change in time spent “OFF” from baseline to the end of 12 weeks double-blind treatment period based on patient diaries.

3.3 Secondary Endpoints

The secondary efficacy endpoints are:

- Percentage of patients with response to therapy, defined as an OFF-time reduction of at least 2 hours, from baseline to end of 12 weeks double-blind treatment period
- Patient Global Impression of Change
- Absolute change in time spent “ON” without troublesome dyskinesia”
- Change in oral L-dopa and L-dopa equivalent dose
- Change in Unified Parkinson’s Disease Rating Scale (UPDRS Part III motor examination) during ON periods
- Change in Quality of Life (using PDQ-8)

3.4 Exploratory Endpoints

The exploratory endpoints are:

- Change in Score of the Non-Motor Symptoms Scale for PD
- Change in MDS-UPDRS Part I patient questionnaire = non-motor experiences of daily living
- Change in MDS-UPDRS II, assessed separately for ON and OFF states
- Change in MDS-UPDRS Part IV fluctuations = 4.3 and 4.4 combined
- Drop-outs due to lack of efficacy
- Beck Depression Scale
- PDSS (PD Sleep Scale)

3.5 Safety Endpoints

The safety endpoints are:

- Evaluation of adverse events and local tolerability
- Skin changes
- Full blood count
- Epworth Sleepiness Scale
- QUIP
- C-SSRS (Columbia- Suicide Severity Rating Scale)

4 TRIAL DESIGN

This clinical trial is designed as a randomized, multicenter, multi-national, parallel-group, double-blind and placebo-controlled phase III study in approx. 102 patients. The trial consists of a double-blind treatment phase followed by an open-label phase.

The study will comprise 2 screening visits to confirm patients' eligibility and their ability to handle diary completion followed by hospital admission at baseline with a maximum stay between 5 and 10 days. In those centres where the established standard practice for apomorphine titration is as an out-patient, Visit 3 may be conducted as day-case hospitalisation. During the 3-month double-blind treatment period, 8 control visits are scheduled. Discontinuation of the blinded drug will be performed at the End of Blinded Treatment Visit. Patients will be offered the possibility to enter the open-label phase starting with the titration of apomorphine at the next visit according to the local standards. The open-label phase is planned for a maximum of 12 months, including 4 control visits after 3, 6, 9and 12 months from commencement of open label treatment and 4 telephone contacts.

All efforts should be made to encourage 12 weeks of blinded treatment. Patients discontinuing the blinded treatment of the study due to lack of efficacy (per investigator discretion) prior week 12 will be offered a possibility to enter the open-label phase.

The study will be performed in hospitals specialized in the treatment of PD.

4.1 Justification of Trial Design

In summary the rationale for the planned clinical trial is to show superiority of the test compound compared to placebo.

The trial design was developed according to the recommendations issued in the current EMA 'Guideline on clinical investigation of medicinal products in the treatment of Parkinson's

disease' (European Medicines Agency (EMA), 2012), The dosage was chosen to reflect the dosages reported in several uncontrolled studies and clinical practice in many centers and countries where apomorphine pump treatment is available. The titration phase was included in the 3-month double-blind treatment period to reduce the burden for patients in the placebo treatment arm.

4.2 Assessments and Examinations

The following assessments and examinations will be performed:

- Patient information and written informed consent at visit V1, V11
- Recording of medical history at visit V1
- Physical examination at visit V1, V3 - V10, V12 - V15
- Vital signs at visit V1, V3-V10, V11 - V15
- Clinical chemistry at visit V1, V3, V6, V8, V10, V12 - V15
- Hematology at visit V1, V3, V6, V8, V10, V12 - V15
- ECG at visit V1, V3, V4, V7, V10, V12 - V15
- Pregnancy Test at visit V1
- Check of inclusion and exclusion criteria at visit V1 and V3
- Assessment of PDQ-8 at visit V3, V7 and V10, V12 - V15
- Diary documentation at visit V1-V7, V10, V12 - 15
- Assessment of MDS-UPDRS at visit V3, V7 and V10, V12 - V15
- Assessment of PGIC at visit V3, V7 and V10, V12 - V15
- Assessment of Non-Motor Symptoms Scale at visit V3, V7 and V10, V12, V15
- Assessment of Beck Depression Scale at visit V3, V7 and V10, V12, V15
- Assessment of QUIP at visit V3, V7 and V10, V12, V15
- Assessment of Epworth Sleepiness Scale at visit V3, V7 and V10, V12, V15
- Assessment of PDSS at visit V3, V7, V10, V12 and V15
- Assessment of C-SSRS at visit V3, V7, V10, V12 - V15
- Randomization to treatment or control group at visit V3
- Training in the infusion system at visit, V3 - V9, V11 - V14
- Handout of IMP to the patients at visit V3 - V9, V11 - V14
- Return of unused IMP at visit V4 - V10 and V12 - V15
- Documentation of changes of the study medication at visit V3 to V15
- Documentation of concomitant therapy and medications taken within 30 days prior to first dose of study therapy at V1
- Documentation of changes in concomitant diseases and medication at visit V3 - V15
- Start of documentation of adverse events at visit V2 (since informed consent), V3 - V15
- Assessment of local and general tolerability at visit V3 - V15

The duration of the apomorphine titration of the open-label phase will be performed according to local standards per investigator discretion.

All study assessments performed during these visits including but not limited to documentation of adverse events, concomitant medication and study drug administration will be documented in the eCRF.

4.3 Assignment of Patients to Treatment Groups

All patients suitable for entry into the trial in the opinion of the Investigator will be recorded in a Pre-Trial Screening Log. Each patient having given consent to participate in the trial will be allocated to an individual patient identification number (Patient ID, consisting of the country code, a two digit site number and an ascending three digit individual number). At the time a Patient ID is allocated to the patient the patient's data (Patient ID, full name and date of birth) will be entered in a confidential Patient Identification Code List / Patient Enrolment Log to allow the Investigator to reveal identity of any patient and to document chronological enrolment of patients by trial number.

4.4 Randomization and Blinding

Patients eligible for treatment will be randomized to one of two treatment arms according to a computer-generated randomization plan in a ratio of 1:1. Placebo infusion will be identical in appearance, packaging and labeling to apomorphine administered by the same pump system. The randomization schedule will be “blocked” to avoid temporal bias.

Patients’ allocation to treatment will take place after completion of all baseline assessments prior to beginning of trial treatment. Randomization and treatment assignment will be performed by fax from/to Sponsor or designee.

The randomization list will be generated by the Biometric Department of ***AMS*** according to the appropriate SOPs. Sealed copies will be stored by the Trial Statistician and the Sponsor/Drug Safety and will not be opened prior to termination of the double-blind phase of the trial, i.e. after data base lock. The Manufacturer for supply of the IMP will receive a copy of the randomization list to ensure proper packaging.

A minimum of 2 investigators are required at each site. If this is absolutely necessary for logistical and staffing reasons, Investigator 2 does not need to be a physician but may be a trained study nurse with experience and training in the performance of the relevant scales, including UPDRS (Table 2).

Table 2 Summary of responsibilities of Investigator 1 and Investigator 2 at each site

Task	Responsibility	
	Investigator 1	**Investigator 2**
Dose changes based on efficacy and adverse events	X	
Review of patient diaries	X	
Take history on efficacy from patients and/or carers	X	
Assessment of tolerability and safety	X	
Assessment of MDS-UPDRS, PGIC		X
Response to any lab changes	X	

Investigator 1 is in charge of the following:

- making dose changes based on efficacy and adverse events,
- reviewing the patient diaries,
- taking the history from patients and/or carers on efficacy,
- assessing tolerability and safety, including checking the state of the abdominal skin, recommending related treatments and including the formal safety assessments review of all safety questionnaires,
- responding to any lab changes.

Investigator 2 performs UPDRS and PGIC questionnaires during double-blind treatment phase.

The patients and carers are advised at the beginning of each study visit not to disclose their medication and not to discuss any local or other adverse reactions to the infusion with Investigator 2. Investigator 2 will not review any lab results.

Investigators must not disclose to the patient or carers if in their judgment the patient is on active drug or placebo and must avoid any comments that might be interpreted as such a judgment.

During the open-label phase either Investigator may perform all assessments

4.5 .Breaking Emergency Codes in Case of Emergency

The Investigator will receive sealed emergency envelopes allocated to his site. Each envelope is labeled with the protocol number and a randomization number. Inside the envelope, the respective IMP is recorded. The Investigator is authorized to unseal the envelope only in case of a medical emergency when adequate treatment of the concerned patient requires immediate knowledge of the actual previous trial treatment. The date of and reason for unblinding must be recorded on the emergency envelope and in the CRF, and should be reported to the Sponsor as soon as possible. During each monitoring visit, the monitor will check whether the emergency envelopes are still intact. All envelopes will be collected as soon as the treatment of all patients at the site is completed.

Further copies of all emergency envelopes are kept at *AMS* Drug Safety Department and STADA Drug Safety Department.

4.6 Planned Number of Trial Sites

A total of about 25 trial sites will be involved in the trial. Each site should include about 3-5 patients to the trial.

5 TIME SCHEDULE / TRIAL DURATION

The overall time schedule for the trial is planned as follows:

First patient in: 1st quarter 2014

Last patient in: 1st quarter 2015

Last patient out (double-blind phase): 2nd quarter 2015

Last patient followed up: 2nd quarter 2016

Each patient will be screened over a period of up to 21 days. The blinded treatment for each patient eligible for trial treatment will be administered over a period of 12 weeks, followed by an open-label phase of 12 months. Open-label study visits will occur at 3, 6, 9, and 12 months from end of blinded treatment, to assess long-term efficacy and tolerability. Thus, the overall trial duration for each patient may be up to 16 months, including screening and the open-label phase.

6 PATIENT POPULATION

Adult male and female patients aged 30 years or older suffering from PD with motor fluctuations not well controlled on medical treatment will be enrolled in the study. If a patient fulfills all of the inclusion criteria and none of the exclusion criteria, his/her eligibility will be assessed during the screening phase and he/she will be randomized to treatment or control in a 1:1 ratio as soon as the randomization criteria are fulfilled, at visit V3. It is expected to randomize 102 patients to either treatment or control group at baseline (V3).

7 SELECTION OF PATIENTS

A patient will only be included in the trial after having given his/her written informed consent. Informed consent will be obtained from the patient himself/herself after having informed him/her of all pertinent aspects of the trial. The investigator will verify that all inclusion and exclusion criteria are met and all other requirements of the trial protocol are fulfilled. He/she will confirm that according to his/her judgment the respective patient is eligible for participation in the trial.

7.1 Inclusion Criteria

The patients will only be included in the trial if they meet all of the following criteria:

- Male or female patients aged ≥30
- Diagnosis of idiopathic Parkinson's disease of >3 years' duration, defined by the UK Brain Bank criteria (with the exception of >1 affected relative being allowed), without any other known or suspected cause of Parkinsonism
- Hoehn & Yahr stage up to 3 in the ON and 2 to 5 in the OFF state
- Motor fluctuations not adequately controlled on medical treatment including L-dopa which was judged by the treating physician to be optimal
- Average of OFF time >= 3 h/day based on screening and baseline diary entries with no day with < 2 hours of OFF time recorded
- Stable medication regimen, with a stable dose of L-dopa administered in at least 4 intakes, for at least 28 days prior to baseline. All oral or transdermal antiparkinsonian drugs are permitted, with the exception of budipine. This regimen may include the use of L-dopa /DDCI rescue medication if this occurs up to 2 times a day, at doses of up to 200 mg L-dopa/day

- Patients must be able to differentiate between the ON and OFF state and between troublesome and non-troublesome dyskinesias
- Male and female patients must be compliant with a highly effective contraceptive method (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method) during the study and for 12 months open-label phase, if sexually active
- Females of childbearing potential must have a negative serum hCG or urine pregnancy test at screening
- Ability to accurately complete a paper diary on designated days (with assistance from caregivers, if required), recording periods when they are “ON without troublesome dyskinesia”, “ON with troublesome dyskinesia”, OFF, and sleeping
- Written informed consent prior to enrolment, after being provided with detailed information about the nature, risks, and scope of the clinical trial as well as the expected desirable and adverse effects of the study treatments
- Patients considered reliable and capable of adhering to the protocol, visit schedule, and medication intake according to the judgment of the investigator

7.2 Exclusion Criteria

The patients will only be included in the trial if they do not meet any of the following criteria:

- History of respiratory depression
- Hypersensitivity to apomorphine or any excipients of the medicinal product
- High suspicion of other parkinsonian syndromes
- Presence of severe freezing or clinically relevant postural instability leading to falls during the ON state
- Concomitant therapy or within 28 days prior to baseline with: apomorphine pen injections; alpha-methyl dopa, metoclopramide, reserpine, neuroleptics, methylphenidate, or amphetamine; intrajejunal L-dopa
- Previous use of apomorphine pump treatment
- History of deep brain stimulation or lesional surgery for PD

- Any medical condition that is likely to interfere with an adequate participation in the study, including e.g. current diagnosis of unstable epilepsy; clinically relevant cardiac dysfunction and/or myocardial infarction or stroke within the last 12 months;
- Symptomatic, clinically relevant and medically uncontrolled orthostatic hypotension;
- Patients with a borderline QT interval corrected for heart rate according to Bazett's formula (QTc) of >450 ms for male and >470 ms for female at screening or history of long QT syndrome; or >450 ms absolute duration;
- Clinically relevant hepatic dysfunction (total bilirubin >2.0 mg/dL, ALT and AST >2 times the upper limit of normal);
- Clinically relevant renal dysfunction (serum creatinine >2.0 mg/dL);
- Pregnant and breastfeeding women;
- Clinically relevant cognitive decline, defined as MMSE ≤24 or according to DSM IV criteria for dementia
- Active psychosis or history of at least moderate psychosis in the past year, or with medically uncontrolled severe depression; very mild illusions or hallucinations in the sense of "feelings of passage or presence" with fully retained insight are not an exclusion criterion.
- Known history of melanoma.
- Any investigational therapy in the 4 weeks prior to randomization.
- History or current drug or alcohol abuse or dependencies

8 TRIAL PROCEDURES AND ASSESSMENTS

8.1 Visit Schedule

During the trial 10 regular trial visits and 5 open-label visits are scheduled. The first screening visit (V1) will be performed at the beginning of the screening period to check the inclusion and exclusion criteria, and the second visit will be performed at the end of the screening period (V2). At the baseline visit (V3) patients will be admitted to hospital and eligibility for entering the treatment phase will be assessed. In those centers / countries, where the standard practice for apomorphine titration is as an out-patient, the V3 may be conducted as day-case hospitalization for a minimum of 8 hours daily.

Seven control visits (V4, V5, V6, V7, V8, V9, V10) will be performed during the double-blind treatment period of 12 weeks.

Five clinic visits (V11, V12, V13, V14, V15) will be performed during the open-label phase of 12 months. Telephone contact will be made with patients between each visit (V11 – V15) for safety monitoring. A final end of study visit (V15) is scheduled at week 52 (+2 weeks), calculated from the beginning of the open-label phase.

The open-label phase commences at V11 with dose titration. The duration of the apomorphine titration of the open-label phase will be performed according to local standards at the discretion of the investigator. All study assessments performed during these visits including but not limited to documentation of adverse event, concomitant medication, and study drug administration will be documented in the eCRF.

Screening Visit V1 (up to 21 days prior to the first application of IMP)

- Patient information and written informed consent
- Recording of medical history
- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- ECG
- Pregnancy test for women of childbearing potential
- Check of inclusion and exclusion criteria
- Instruction on diary completion and documentation of motor phases by investigator and patient
- Handover of patient diaries
- Documentation of concomitant therapy and medications taken within 30 days prior to first dose of study therapy

Screening Visit V2 (up to 14 days prior to the first application of IMP)

- Review of diary documentation and training in completion
- Documentation of adverse events since informed consent

Optional Screening Visit (to be performed in case diary was not adequately completed at V2)

- Review of diary documentation
- Documentation of adverse events

Assessment of Eligibility for Treatment / Randomization

The patient's eligibility will be assessed and the patient will be randomized as soon as all screening assessments have been performed, all necessary data are available and the randomization criteria are fulfilled. During this baseline visit the following tasks will be performed:

The in-patient stay (or day-case hospitalization *for a minimum of 8 hours daily in centers where this is the standard practice*) is scheduled to be 5 days and can be extended up to 10 days if necessary.

Visit V3 (Day 0 to Day 4 + 5 days)

Hospital admission:

- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- ECG
- Check of inclusion and exclusion criteria
- Assessment of PDQ-8
- Review of diary documentation
- Assessment of MDS-UPDRS
- Assessment of PGIC
- Assessment of Non-Motor Symptoms Scale
- Assessment of Beck Depression Scale
- Assessment of QUIP
- Assessment of Epworth Sleepiness Scale
- Assessment of PDSS (PD Sleep Scale)
- Assessment of C-SSRS (Columbia Suicide-Severity Rating Scale)
- Randomization to treatment or control group
- Documentation of adverse events

During in/out-patient stay:

- Training on the infusion system
- Administration of IMP to the patients
- Documentation of dose changes of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Daily diaries from Day 2 to discharge

At the end of in/out-patient stay (day of discharge)

- Physical examination
- Vital signs
- ECG
- Review of diary documentation
- Handout of IMP to the patients
- Training on infusion system (if needed)
- Documentation of dose changes of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Double Blind Treatment Period

During the double-blind treatment period the following visits with the respective tasks will be performed:

Visit 4 (Day 14 ± 3 days) and Visit 5 (Day 21 ± 3 days)

- Physical examination
- Vital signs
- ECG (only Visit 4)
- Review of diary documentation
- Training on the infusion system (if needed)
- Handout of IMP to the patients
- Return of unused IMP
- Documentation of dose changes of IMP
- Adjustments in and documentation of concomitant medication
- Documentation of changes in concomitant diseases
- Documentation of adverse events
- Assessment of local and general tolerability

Visit 6 (Day 28 ± 3 days)

- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- Review of diary documentation
- Training on the infusion system (if needed)
- Handout of IMP to the patients
- Return of unused IMP
- Documentation of dose changes of IMP
- Adjustments in and documentation of concomitant medication

- Documentation of changes in concomitant diseases
- Documentation of adverse events
- Assessment of local and general tolerability

Visit 7 (Day 42 ± 3 days)

- Physical examination
- Vital signs
- ECG
- Assessment of PDQ-8
- Review of diary documentation
- Assessment of MDS-UPDRS
- Assessment of PGIC
- Assessment of Non-Motor Symptoms Scale
- Assessment of Beck Depression Scale
- Assessment of QUIP
- Assessment of Epworth Sleepiness Scale
- Assessment of PDSS (PD Sleep Scale)
- Assessment of C-SSRS
- Training on the infusion system (if needed)
- Handout of IMP to the patients
- Return of unused IMP
- Documentation of dose changes of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Visit 8 (Day 56 ± 3 days)

- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- Training on the infusion system
- Handout of IMP to the patients
- Return of unused IMP
- Documentation of dose changes of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Visit 9 (Day 70 ± 3 days)

- Physical examination
- Vital signs
- Training on the infusion system (if needed)
- Handout of IMP to the patients
- Return of unused IMP
- Documentation of changes of the IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Visit 10 (Day 84 ± 3 days) – End of double blinded treatment or at early termination

- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- ECG
- Assessment of PDQ-8
- Review of diary documentation
- Assessment of MDS-UPDRS
- Assessment of PGIC
- Assessment of Non-Motor Symptom Scale
- Assessment of Beck Depression Scale
- Assessment of QUIP
- Assessment of Epworth Sleepiness Scale
- Assessment of PDSS (PD Sleep Scale)
- Assessment of C-SSRS
- Return of unused IMP
- Discontinuation of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Open-Label PhaseVisit 11 (V10 +1 to 3 days) Dose adjustment
Start of open-label phase, start of new dose titration of apomorphine

The duration is determined by the investigator`s decision and local treatment standards**.** All efforts should be made to start the open-label phase on the day following the end of blinded treatment visit. In exceptional cases, up to 3 days are acceptable. All visits in the open-label phase are calculated from the first day of V11.

- Patient information and written informed consent
- Vital Signs
- Training on the infusion system (if needed)
- Handout of IMP to the patients
- Documentation of dose changes of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Visit 12 (V11 + 12 weeks ± 2 weeks), Visit 13 (V11 + 24 weeks ± 2 weeks), Visit 14 (V11 +36 weeks ± 2 weeks)

- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- ECG
- Assessment of PDQ-8
- Diary documentation
- Assessment of MDS-UPDRS
- Assessment of PGIC
- Assessment of Non-Motor Symptoms Scale (Visit 12 only)
- Assessment of Beck Depression Scale (Visit 12 only)
- Assessment of QUIP (Visit 12 only)
- Assessment of Epworth Sleepiness Scale(Visit 12 only)
- Assessment of PDSS (Visit 12 only)
- Assessment of C-SSRS
- Training on the infusion system (if needed)
- Handout of IMP to the patients
- Return of unused IMP
- Documentation of dose changes of IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

Interim telephone contact

Telephone calls should be made to patients between each of the 12 weekly visits. Suggested weeks for the telephone call are calculated from the date of V11.

Visit 11a (week 6 ± 1 week), Visit 12a (week 18 ± 1 week), Visit 13a (week 30 ± 1 week) and Visit 14a (week 44 ± 1 week)

- Telephone call to patient
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events

End of Study

Visit 15 (V11 + 52 weeks + 2 weeks) or at early termination of the open-label phase

- Physical examination
- Vital signs
- Clinical chemistry
- Hematology
- ECG
- Assessment of PDQ-8
- Diary documentation
- Assessment of MDS-UPDRS
- Assessment of PGIC
- Assessment of Non-Motor Symptoms Scale
- Assessment of Beck Depression Scale
- Assessment of QUIP
- Assessment of PD Sleep Scale
- Assessment of Epworth Sleepiness Scale
- Assessment of PDSS
- Assessment of C-SSRS
- Return of unused IMP
- Documentation of dose changes of the IMP
- Documentation of changes in concomitant diseases and medication
- Documentation of adverse events
- Assessment of local and general tolerability

8.2 Patient Diary and Questionnaires

Several questionnaires will be filled out during the study.

8.2.1 Patient Diary

Screened and eligible patients will be instructed on the diary procedures.

A Patient Diary will be handed over at Screening Visit 1 for the documentation for each half hour of: sleep / OFF / ON without dyskinesia / ON with non-troublesome dyskinesia / ON with troublesome dyskinesia.

Patients receive instruction on the completion of the diaries from the investigators, using each patient´s individual parkinsonian symptoms to define a patient´s OFFs.

During Screening Visit 1, the investigators will observe the patient in both the “ON” and “OFF” state while the patient completes a diary for at least 2 hours. If no switch from ON to OFF or from OFF to ON occurs during these 2 hours, the observation time will be extended until a switch occurs. Concordance between patients´ self-assessment and the investigator´s assessment of ON and OFF periods needs to be present in at least 3 out of 4 observed half hour periods.

Patient diaries are returned at Screening Visit 2. The number of missing items or double entries may not exceed 2 hours / day. If patient diaries are incompletely or incorrectly completed, training may be repeated during another observation period on that day and a new set of diaries will be handed over.

Patients are asked to complete diaries:

- for 2 days prior to Screening visit 2, optional screening visit and Baseline,
- every day, starting from day 2, during Visit 3,
- for 2 days prior to each clinic visit at V4, V5 and V6 (these diaries serve as one source of information on which any treatment changes are based) and, during the stable treatment phase, at V8 and V10. During the open-label phase at weeks 12 (V12), 24 (V13), 36 (V14) and 52 (V15) calculated from V11.

Patients will be asked to keep daily records of infusion times from V3 – V10.

8.2.2 Questionnaires

8.2.2.1 Quality of Life Questionnaire (PDQ-8)

The Parkinson's Disease Quality of Life Questionnaire is a self-reported PD specific health status questionnaire to assess the impact of PD. The PDQ-39 consists of 39 questions with 8 discrete scales.

- mobility
- activities of daily living
- emotional well-being
- stigma
- social support
- cognitions
- communication
- bodily discomfort

A short form of the PDQ-39 is the PDQ-8 (Jenkinson et al., 1997). The PDQ-8 contains 8 of the 39 items of the PDQ-39; one item selected from each of the 8 scales.

The questions are responded to using one out of five grades, according to how often (from never to always) the patient has experienced the problem during the past month.

8.2.2.2 Unified Parkinson`s Disease Rating Scale (MDS-UPDRS)

The MDS-UPDRS is a revision of the UPDRS (Goetz et al., 2007). It consists of 4 parts (Non-motor Experiences of Daily Living, Motor Experiences of Daily Living, Motor Examination, Motor Complications) with a total summed score. Part 1A, III and IV are completed by Investigator 2. The patient completes Part 1B and II.

Interpretation

All items have five response options from 0=normal to 4=severe (Goetz et al., 2007). Higher scores reflect worsening disability.

8.2.2.3 Patient`s Global Impression of Change (PGIC)

The patient' global impression of change (PGIC) score is an anchor-based method. Here, the patient ranks their change following an intervention on a scale from 1 to 7, with 1 representing "no change" and 7 representing "a great deal better". The a priori definition of clinically significant change suggests that PGIC values of 6 or more correlate best with actual change.

8.2.2.4 Non-Motor Symptoms Scale

The non-motor symptoms scale (NMSS), consisting in 30 items instrument, is rated by clinicians, to explore 9 domains (cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual dysfunction, and miscellaneous) (Chaudhuri et al., 2007). Items are scored for frequency and severity. NMSS is specifically designed for the comprehensive assessment of non-motor symptoms in patients with PD.

8.2.2.5 Beck Depression Inventory

Beck Depression Inventory is a self-reported test consisting of 21 questions. These questions cover various situations a patient is likely to experience in daily life.

Interpretation

Each question is answered based on a score value from 0 to 3. A value of 0 indicates that the patient is feeling fine, whereas a 3 indicates a patient feeling sad. After completion, the values are tallied up and measured against a scale:

0-13: minimal depression

14-19: mild depression

20-28: moderate depression

29-63: severe depression

8.2.2.6 Questionnaire for Impulsive-Compulsive Disorders in Parkinson`s Disease (QUIP, long form)

The QUIP is a brief self-assessment screening instrument consisting of 3 sections. Section 1 assesses impulse control disorders (ICDs), Section 2 other compulsive behaviors and Section 3 compulsive medication use (Weintraub et al., 2009).

Interpretation

A score of 1 or higher on any item indicates the presence of ICD.

8.2.2.7 Epworth Sleepiness Scale

The Epworth Sleepiness Scales (ESS) is a self-administered questionnaire measuring daytime sleepiness on a scale of increasing probability from 0 to 3 for 8 different situations.

Interpretation

The scores are summarized. A number in the 0–9 range is considered to be normal, whereas a number in the range of 10–24 indicates that expert medical advice should be sought (Johns, 1991).

Additional Sleep Episode Question

An additional question will be added: Since your last visit (or in the past month if baseline visit), have you had any episodes of unintended and unwanted falling asleep in undesirable situations (e.g., operating machinery, driving a car)? If yes, please, describe each episode.

8.2.2.8 PD Sleep Scale (PDSS)

The Parkinson's Disease Sleep Scale (PDSS) is an instrument for quantifying sleep problems in Parkinson's Disease. The PDSS is a frequency measure scale with five categories commonly associated with sleep disturbance in PD (Trenkwalder et al., 2011).

8.2.2.9 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) is a rater based interview assessment tool that evaluates suicidal ideation and behavior.

The C-SSRS questionnaire includes five subtypes of suicidal ideation, five subtypes of suicidal behavior, and self-injurious behavior without suicidal intent as a standard (Posner et al., 2011).

The Baseline questionnaire will be administered at V3, to determine lifetime suicidality, with the Since Your Last Visit questionnaire used at each subsequent assessment point.

8.3 Physical Examination

The physical examination should include the examination of the following body systems:

- Central and peripheral nervous system
- Cardiovascular system
- Respiratory system
- Gastro-intestinal system
- Endocrine system
- Sensoric system
- Skin
- Others (e.g. infections, allergies)

8.4 Vital Signs

The following vital signs will be assessed during the study:

- Pulse – measured supine and standing
- Orthostatic Blood Pressure Measurement – supine blood pressure (after 5 minutes rest) followed by standing blood pressure (within 1 – 3 minutes of standing). The Visit 3 assessment will be an average of three supine and three standing measurements. All other visits will be single supine and single standing measurements

During Visit 3 orthostatic BP measurements should be taken 75 to 90 minutes after each dose increase.

During double-blind treatment (V4 to V10) single readings of orthostatic BP measurements will be taken at the clinic, after start of infusion which patient manages at home.

During open label phase (V11 to V15) single readings of orthostatic BP measurements will be taken at the clinic, after start of infusion which patient manages at home.

8.5 Laboratory Test

The laboratory tests include the following parameters:

Biochemistry: Tests include sodium, potassium, urea, creatinine, glucose, total protein, albumin, uric acid, AST, ALT, alkaline phosphatase, total bilirubin, lactate dehydrogenase, calcium, cholesterol, triglycerides and haptoglobin.

Hematology: Tests include a complete blood count with differential, white blood cell count, and platelet count.

The analysis of the blood samples will be performed applying the blood sampling system and the methods of analysis routinely used by the Investigator. Valid laboratory normal ranges including the units of measurement for all parameters requested by the protocol and laboratory certificates will be obtained from the trial site.

All values will be judged by the Investigator as normal, abnormal without clinical relevance or abnormal with clinical relevance. All values judged as abnormal with clinical relevance should be commented by the Investigator and will be documented as adverse events.

8.6 Pregnancy Test

For women of childbearing potential a serum hCG or urine pregnancy test must be performed at screening (Visit V1) and will be repeated as often as needed according to local requirements to ensure that no pregnant women are included in the trial.

Male and female patients must use a highly effective contraceptive method (oral hormonal contraception alone is not considered highly effective and must be used in combination with a barrier method) during the main study and the 12 months open-label phase, if sexually active.

9 INVESTIGATIONAL MEDICINAL PRODUCT

9.1 Description of the Investigational Medicinal Products

Apomorphine hydrochloride 5 mg/ ml solution is manufactured by Catalent Pharma Solutions (Brussels, Belgium) on behalf of the Sponsor. Apomorphine is supplied as solution for infusion in a 10 ml glass pre-filled syringe. Each 10 ml pre-filled syringe contains 50 mg apomorphine hydrochloride. 1 ml contains 5 mg apomorphine hydrochloride.

The active ingredient is apomorphine hydrochloride. Other constituents are sodium metabisulphite (E223), hydrochloric acid, concentrated (for pH adjustment) and water for injection.

Placebo is saline infusion manufactured by Catalent Pharma Solution (Brussels, Belgium) and is identical to apomorphine in appearance, weight and will be provided for use in the study in the same pre-filled syringes as apomorphine.

The Canè CRONO APO-Go infusion pump will be used to administer the apomorphine or placebo infusion (and bolus doses during the open label phase, if required).

9.2 Packaging and Labeling of IMPs and Pump System

All medication in this trial will be prepared, packed and labeled under the responsibility of a qualified person of the Sponsor or designee in accordance with Good Manufacturing Practice (GMP) and all applicable local laws and regulations. The trial medication for each patient will be packed in cartons holding a tray with 10 syringes.

The labeling will be designed in compliance with the applicable national laws. A booklet label in all study languages will be used for the syringes and cartons. A sample of the labels will be archived in the Trial Master File.

The Sponsor will provide an appropriate number of infusion pumps (Canè CRONO APO-Go) and infusion-related materials (including 20-mL plastic syringes, luer connectors, and infusion lines) to the study site for dispensing to patients as needed. Pumps will be provided to patients in their commercial packaging.

9.3 Storage Conditions and Stability of Apomorphine

All supplies must be stored in a secure, limited-access storage area. Apomorphine must not be stored above 25°C. The pre-filled syringe should be kept in the outer carton in order to protect from light.

Any deviations from the recommended storage conditions must be reported immediately to the Sponsor. Use of the affected IMP should be suspended until authorization for its continued use has been received from the Sponsor.

9.4 Preparation and Handling of Apomorphine

The IMP may be distributed by the Investigator or by a member of staff specifically authorized by the Investigator.

Prior to the start of treatment and throughout Visit 3, the patients and/or carers will be trained in the use of the apomorphine infusion system by the study personnel. The Sponsor will provide an adequate number of appropriate training materials (e.g., manuals) for retention at the site and distribution to patients.

9.5 Investigational Medicinal Products Accountability

The Investigator is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of drug records.

- Upon receipt of IMP the Investigator (or pharmacist) will check for accurate delivery and acknowledge receipt by signing and dating the documentation provided by the Sponsor or designee. A copy of each document will be filed in the Trial Master File and another copy be retained for the Investigator Site File.
- The dispensing of the IMP will be carefully recorded at the site on the appropriate drug accountability forms provided by the Sponsor and an accurate accounting will be available for verification by the monitor at each monitoring visit.
- IMP accountability records will include:
  - Confirmation of IMP delivery to the trial site
  - The inventory of IMP at the site provided by the Sponsor
  - The dispensing to each patient
  - The disposition of unused IMP
  - Dates, quantities, batch numbers, expiry dates and the Pat. IDs assigned
- The Investigator should maintain records that adequately document:
  - The patients were provided the doses specified by the protocol/amendment(s)
  - All IMP provided by the Sponsor were fully reconciled

Patients should be instructed to bring with them to each visit all unused packages of IMP, in order to allow the assessment of compliance with trial treatment.
IMP that has been dispensed to a patient must not be re-dispensed to a different patient. Unused IMP must not be discarded or used for any purpose other than the present trial.

The monitor will periodically collect the IMP accountability forms and check all IMP returns (unused syringes) prior to making arrangements for authorizing their destruction by the trial site or their return to the Sponsor.

10 TREATMENTS ADMINISTERED

10.1 Pre-Treatment, Trial Medication and Adjustments in Oral/Transdermal Antiparkinsonian Medication

10.1.1 Pre-treatment Prior and During Hospitalization

Antiemetic premedication will be administered according to local standards. Recommended pre-treatment use of domperidone is 10 mg tid starting 3 days prior to the infusion. ECGs will be repeated at Baseline and at hospital discharge. If these ECGs show QTc > 430 ms for male and >450 ms for female, domperidone can be reduced stepwise to 10 mg bid or totally withdrawn, at the discretion of the investigator. ECG will be repeated at V4. It is recommended to perform ECG before and after any dose increase of domperidone, per investigator discretion. At any time if QTc is > 450 ms, a cardiology opinion must be obtained and the decision for continuation or discontinuation of domperidone treatment (QTc > 430 ms for male and >450 ms for female) should be made in accordance with the cardiologist.

10.1.2 Trial Medication and Adjustments in Oral/Transdermal Antiparkinsonian Medication

The hourly flow rate is adjusted during Visit 3 and during the first 4 weeks of double-blind treatment, to doses of 3 mg/hour up to 8 mg/hour, depending on individual tolerability and efficacy.

The target dose is each patient´s individual optimized dose or the maximum dose of 8 mg/hour.

Patients will be admitted to hospital on the day of the Baseline visit V3. In those centres where the established standard practice for apomorphine titration is as an out-patient, Visit 3 may be conducted as day-case hospitalisation, for a minimum of 8 hours daily. Patients admitted as day-cases (in those centres where titration is done on an out-patient basis as established standard practice) must have a live-in carer or spouse

On the day of hospital / first day case admission, patients will be on their regular medical treatment. On the day following Baseline, patients will take their regular medication and the pump will be initiated.

Each patient will receive a starting dose for apomorphine or placebo as subcutaneous infusion of 1 mg/hour during the first day of infusion.

If no adverse effects occur, the hourly flow rate will then be increased in the following manner:

- During in-patient / day case stay the hourly flow rate will be increased daily by 0.5-1.0 mg/hour until the maximum dose of 8 mg/hour or the highest tolerated dose has been reached, whichever occurs first.
- At the weekly visits up to Visit 6, the hourly flow rate will be increased by 0.5 to 1 mg/hour per visit until the maximum dose of 8 mg/hour or the highest tolerated dose has been reached, whichever occurs first.

A gradual reduction of concomitant medication is driven by the occurrence of possible adverse events (AEs). During the titration phase (i.e. in the first 4 weeks) concomitant antiparkinsonian medication can be reduced in case of newly emergent or worsened dopaminergic AEs – in particular dyskinesias, nausea, orthostatic hypotension, or sleepiness. Therefore, if dopaminergic adverse effects occur, concomitant medication should be decreased first and the study drug flow rate should be maintained. Upon resolution of the adverse event, the next increase in flow rate should be undertaken.

The investigator will adjust concomitant treatment in a hierarchical way, aiming at the reduction and discontinuation of any oral/transdermal dopamine agonist first. A sufficiently high levodopa dose must be maintained in the morning to ensure patients reach an ON state that will allow them to manage the pump.

The oral/transdermal treatments are reduced / discontinued in this order:

Dopamine agonists
Discontinue gradually, starting after apomorphine initiation, aiming at discontinuation by the time of discharge from the hospital in those patients where this is possible and where increasing flow rates of the study drug have led to AEs. The speed and degree of reduction are left to the judgment of the investigator and are guided by the emergence of dopaminergic AEs.

MAO B inhibitors
Discontinue (gradually if applicable) after oral / transdermal dopamine agonists have been discontinued, if applicable.

L-dopa
Decrease gradually after oral / transdermal dopamine agonists and MAO B inhibitors have been discontinued (if applicable). Decrease individual doses first, and then decrease number of intakes. L-dopa doses should not be discontinued in the morning or at night time (i.e. before and after the use of the infusion). To ensure an ON state in the early morning, the morning levodopa dose needs to be determined individually during the blinded phase and may exceed the levodopa dose or the levodopa equivalent of the early morning dose prior to entry into the trial and may include dispersible levodopa at the discretion of the investigator. This may be required in but is not limited to patients who were initially on long-acting

dopamine agonists. The aim is to achieve a full ON state that will allow the patients to receive instructions on pump handling and the eventually take over the handling of their pump. For day-case patients, the morning levodopa dose will need to be sufficiently high to enable travelling to the clinic.

If patients use fixed combinations of L-dopa/ carbidopa/ entacapone, this combination should be used at decreasing L-dopa doses. If patients use entacapone as separate tablets or tolcapone, these should be discontinued before L-dopa doses are changed.

Amantadine, anticholinergics

Patients who are on amantadine or anticholinergics will continue on the same dose throughout the study.

These changes in the medication will be done while patients are in-patients and – if necessary - at the weekly visits up to Visit 6. Additional, unscheduled visits may become necessary and if these occur before Visit 6, the hourly flow rate and medication may also be adjusted.

The oral/transdermal treatment must not exceed pre-study doses and no new oral /transdermal antiparkinsonian drugs may be introduced during the study.

All concomitant medication and apomorphine should be maintained stable after Visit 6 and may only be adjusted if clinically necessary due to lack of effect or adverse events.

10.1.3 Daily Duration of Pump Treatment

From the day following Baseline onwards, the regular duration of daily pump treatment should be aimed at. On the day after Baseline, the pump should be initiated in the morning. The aim is to have the pump in use for 16 hours from day 2 of the in-patient stay. A range of 14-18 hours is acceptable if necessary. Only in exceptional circumstances, a 12 hour target cycle is permitted. The reason for a target cycle below 16 hours must be documented. This may be the case due to carer availability or, rarely, a patient´s personal circumstance (such as early bed time). In patients who are initiated as day cases, the daily duration of infusion may be shorter during the day case phase until patients have learned how to remove the pump. The minimum duration during Visit 3 is 8 hours daily.

Training in pump handling and skin care:

Prior to the study start, the pump will be demonstrated to patients and carers and the basic principles of handling are explained. Throughout the in-patient stay, the patients and/or

carers will be trained in the use of the apomorphine infusion system and skin care by the study personnel.

Duration of in-patient / day case stay:

The in-patient stay (or day case phase if applicable) is scheduled to be 5 days (with discharge at the end of day 5, i.e. after 4 nights) and can be extended up to 10 days if necessary.

10.1.4 Treatment of Nocturnal OFFs:

For nocturnal OFFs, L-dopa with or without a COMT inhibitor or L-dopa CR may be used, including late at night and during the night if necessary.

Patients should remain on their previous nighttime medication schedule as closely as possible.

Patients with new night time OFF symptoms who were on long acting dopamine agonists before entry and whose dose has been reduced may resume the lowest dose of the respective long acting dopamine agonist that restores nocturnal mobility (administered at night time), if night time L-dopa (COMT inhibitor) does not sufficiently improve night time mobility.

Patients who were on 24 hour rotigotine before entry may use rotigotine at nighttime up to the same dose (patch size) as before entry. No new dopamine agonists may be introduced, such as transdermal rotigotine during night time.

10.2 Transition from Double-Blind to Open Label Phase

At the end of blinded treatment visit (Visit 10) (week 12 for completers or earlier for drop-outs) double-blind study medication will be discontinued. Ongoing oral / transdermal medication will be continued after discontinuation of the study drug. Any additional dopaminergic supplementation that may be required will be given as L-dopa, as per investigator discretion and based on the L-dopa equivalent dose of each patient´s oral/transdermal medication dosages at baseline.

Patients will be offered the possibility to enter the open–label phase starting with the titration of apomorphine according to the local standards. All efforts should be made to start the open-label phase on the day following end of double blinded treatment visit. In exceptional cases up to 3 days are acceptable. The starting dose for apomorphine is 1 mg/hour. Concomitant medication will be adjusted as per discretion of the investigator. Use of bolus function of the pump and bolus doses are not limited during this phase of the study.

10.3 Permitted Medication

Any medications other than those excluded by the protocol that are considered necessary for the patient's welfare and will not interfere with the trial medication may be given at the discretion of the Investigator. The Investigator will record all concomitant medications taken by the patient during the trial from the date of signature of informed consent, in the appropriate section of the CRF.

10.3.1 Rescue Medication

During the adjustment period (4 weeks), any use of rescue medication should strongly encourage the investigator to increase the hourly flow rate of apomorphine, except when this is not possible due to adverse effects. The aim is to reach a stable state without the use of rescue doses above predefined doses.

During the in-patient / day case stay and up to Visit 6, oral L-dopa (dispersible or regular) may be used at doses of up to 300 mg /day. After that, the maximum daily number of rescue L-dopa doses is 2, with a maximum daily dose of 200 mg.

During the double-blind study phase, the bolus function of the pump is not permitted.

If oral L-dopa rescue doses have been part of a patient´s pre-study stable regime, they may be continued during the study, provided their total daily dose does not exceed the rescue medication the patient used before entry.

10.4 Prohibited Medication

10.4.1 Treatment for Parkinson`s Disease

Concomitant treatment with budipine, apomorphine pen injections, alpha-methyl dopa, metoclopramide, reserpine, neuroleptics, methylphenidate, or amphetamine; intrajejunal L-dopa is forbidden throughout the study.

10.4.2 Experimental Drugs or Treatment

Use of concomitant experimental drugs or treatments is prohibited within 4 weeks prior to randomization and throughout the trial. If a patient needs to receive an experimental drug or treatment in addition to the trial IMP, the patient should not receive any additional dose of the trial IMP and should be discontinued from this trial immediately.

10.5 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in the protocol. Any overdose must be recorded in the IMP section of the CRF.

There is little clinical experience of overdose with apomorphine by this route of administration. Symptoms of overdose may be treated empirically as follows:

- Excessive emesis may be treated with domperidone
- Respiratory depression may be treated with naloxone
- Hypotension: appropriate measures should be taken, e.g. raising the foot of the bed
- Bradycardia may be treated with atropine.

11 RISKS, SIDE EFFECTS AND PRECAUTIONS

11.1 Known Risks and Side Effects

11.1.1 Risks and Side Effects of Apomorphine Administration

Apomorphine hydrochloride should be given with caution to patients with renal, pulmonary or cardiovascular disease and persons prone to nausea and vomiting.

Extra caution is recommended during initiation of therapy in elderly and/or debilitated patients.

Since apomorphine may produce hypotension, even when given with domperidone pretreatment, care should be exercised in patients with pre-existing cardiac disease or in patients taking vasoactive medicinal products such as antihypertensives, and especially in patients with pre-existing postural hypotension (Licher MT GmbH, 2012).

Since apomorphine, especially at high dose, may have the potential for QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia (Licher MT GmbH, 2012).

Apomorphine may be associated with local subcutaneous effects. Most patients experience injection site reactions, particularly with continuous use. These may include subcutaneous nodules, induration, erythema, tenderness and panniculitis. Various other local reactions (such as irritation, itching, bruising and pain) may also occur.

These can sometimes be reduced by the rotation of injection sites or possibly by the use of ultrasound (if available) to areas of nodularity and induration.

Hemolytic anemia and thrombocytopenia have been reported in patients treated with apomorphine. Hematology tests should be undertaken at regular intervals. Caution is advised when combining apomorphine with other medicinal products, especially those with a narrow therapeutic range.

Neuropsychiatric problems co-exist in many patients with advanced PD. There is evidence that for some patients neuropsychiatric disturbances may be exacerbated by apomorphine. Special care should be exercised when apomorphine is used in these patients.

Apomorphine has been associated with somnolence, and other dopamine agonists can be associated with sudden sleep onset episodes, particularly in patients with PD. Pathological gambling, hypersexuality and impulsive eating or buying have been reported in patients treated with dopamine agonists for PD, including apomorphine.

Apomorphine (APO-Go PFS) 5 mg/ml solution for infusion in pre-filled syringe contains sodium metabisulphite which may rarely cause severe allergic reactions and bronchospasm.

11.2 Precautions and Preventive Measures

The abdominal skin must be checked at each visit. Any skin changes must be documented (counted and described).

Indurations:

- Number
- Size
- Signs of inflammation in these:
    - If yes, in how many
    - Degree of inflammation: mild, moderate or severe

Ulcerations

Necrosis

Abscess

Before starting the infusion and at each visit, patients are to be reminded of the following measures:

- strict hygiene,
- massages after removing the needle,
- rotation of insertion site, making use of the whole abdomen (if comfortable to the patient),
- do not leave needle in for >18 hours.

If nodule formation is suspected to interfere with the absorption of the study drug, patients should be re-trained in identifying suitable insertion sites. When necessary and depending on local availability, the following additional methods are permitted:

- ultrasound,
- silicone patches or

- massage devices including creams, as recommended by the national provider of apomorphine or by national treatment guidelines.

Laboratory tests are performed at Screening, Baseline (V3) and at V6, V8 and V10 and during open-label V12, V13, V14 and V15. These will include full blood count with differential blood count, haptoglobin, bilirubin and LDH.

In the case of a drop of hemoglobin by ≥1.5 g/dl compared to the previous test, hemolytic anemia must be ruled out. The urgency of intervention depends on the degree of the change and whether there are any concomitant laboratory changes suggestive of hemolytic anemia and must be judged by the investigator in charge of reviewing the blood test results.

The patient must be asked to come for an unscheduled safety visit and have the following assessments:

- clinical assessment for symptoms and signs of anemia,
- full blood count with differential blood count,
- Coombs test,
- haptoglobin,
- bilirubin,
- LDH.

If any findings suggest hemolytic anemia, an internist / hematologist must be consulted. If hemolytic anemia is confirmed, apomorphine must be stopped and the patient must be managed as advised by the consulted internist / hematologist. The patient must be discontinued from the study.

11.3 Anticipated Benefits

For the patients randomized to treatment the benefit lies in the possibility of a positive therapeutic effect, and with their participation in the trial all patients contribute to the scientific understanding of the properties and impacts of apomorphine.

11.4 Risk-Benefit-Assessment

This trial is designed as a Phase III trial but performed as a Post-Marketing trial in all participating countries.

The proposed treatment in the active group is in full accordance with the labeled use of Apo-Go 5mg/ml infusion in Parkinson's disease. The inclusion and exclusion criteria are not exceeding the labeled use of the test product.

Thus the main risk for the patient participating in this trial is the treatment with placebo for 12 weeks. However, the active and placebo treatments are considered principally as add-on

treatments with subsequent adaptation of the baseline medication. Thus, the risk for patients under additional placebo treatment is limited. Patients who participated in the trial in the placebo arm are free to be treated with the product during the open-label phase, except the patient discontinued for safety reasons.

The trial itself does not put the patient on further investigational risks, e.g. due to further invasive investigations etc.

12 SAFETY REPORTING

Comprehensive assessments of any apparent toxicity experienced by the patient will be performed throughout the course of the trial from the time of patient's signature of informed consent. Trial site personnel will report any Adverse Event (AE), whether observed by the Investigator or reported by the patient (see section 12.2.1 Eliciting Adverse Events).

The safety profile of apomorphine will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events, physical examination findings including vital signs and laboratory tests.

12.1 Definitions and Guidelines

12.1.1 Adverse Event (AE) and Adverse Reaction (AR)

An adverse event is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

Adverse Events may include the following types of occurrences:

- Suspected adverse reactions
- Other medical experiences, regardless of their relationship with the Investigational Medicinal Product, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing or physical examination findings
- Reactions from IMP overdose, abuse, withdrawal, sensitivity, toxicity or failure of the IMP's expected pharmacological action

Those medical conditions related to the disease under study whose changes during the trial are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the investigational medicinal product, are NOT considered as AEs and should not be recorded in the CRF. All other medical conditions which are present at baseline should not be considered as AEs unless a worsening has occurred (see section 13.1.4).

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

An adverse reaction of an investigational medicinal product is any untoward and unintended response to an investigational medicinal product related to any dose administered. All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

An unexpected adverse reaction is an adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or Summary of Product Characteristics (SmPC) for an authorized product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

12.1.2 Serious Adverse Event (SAE) and Serious Adverse Reaction (SAR)

A serious adverse event (SAE) or serious adverse reaction (SAR) is any untoward medical occurrence or effect that at any dose

Results in death
i.e. the AE causes or contributes to the death.

Is life-threatening
i.e. an AE in which the patient was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Requires hospitalization or prolongation of existing hospitalization
i.e. the AE requires at least a 24-hour inpatient hospitalization or prolongs a hospitalization beyond the expected length of stay. Hospital admissions for surgery planned before trial entry, for social reasons or for normal disease management (including treatment adjustment) are NOT to be considered as SAE according to this criterion.

Results in persistent or significant disability or incapacity
i.e. the AE resulted in a substantial disruption of the patient's ability to conduct normal activities.

Is a congenital anomaly or birth defect
i.e. an adverse outcome in a child or foetus of a patient exposed to the Investigational Medicinal Product before conception or during pregnancy.

Is a medically important condition
Medical judgment should be exercised in deciding whether an adverse event/reaction is serious in other situations. Important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

Any serious adverse event occurring during the trial must be reported, whether considered treatment-related or not.

12.1.3 Abnormal Laboratory Findings and Other Objective Measurements

Abnormal laboratory findings and other objective measurements should NOT be routinely captured and reported as AEs as they will be recorded and analyzed separately. However, abnormal laboratory findings or other objective measurements that meet the criteria for a Serious Adverse Event (SAE), result in discontinuation of the Investigational Medicinal Product, require medical intervention or are judged by the Investigator to be clinically significant changes from baseline values should be captured and reported on the AE pages of the CRF.

When reporting an abnormal laboratory finding on the AE pages of the CRF, a clinical diagnosis should be recorded rather than the abnormal value itself, if this is available (for example, “anemia” rather than “decreased red blood cell count” or “hemoglobin = 10.5 g/dL”).

12.1.4 Baseline Medical Conditions

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered adverse events. These medical conditions should be adequately documented on the medical history page of the CRF. However, baseline medical conditions, other than the disease under study, that worsen in severity or frequency during the trial should be recorded and reported as adverse events.

12.1.5 Exacerbation of Disease under Study

In this protocol, symptoms and signs of exacerbation or worsening of **Parkinson’s disease** will usually be captured in the context of efficacy assessment, and recorded on Investigator’s or patient’s assessment pages of the CRF. Therefore, symptoms, exacerbation or worsening of **Parkinson’s disease,** even if hospitalization was necessary, will not be considered as adverse events nor captured on the AE page of the CRF unless the event is considered possibly or

probably related to the investigational product (i.e. worsening is not consistent with the anticipated natural progression of the disease).

12.2 Adverse Events Reporting

12.2.1 Eliciting Adverse Events

Data on adverse events will be obtained at scheduled or unscheduled trial visits, based on the constant survey of the patient's state of health by the Investigator and on information spontaneously provided by the patient and/or through questioning of the patient. Adverse event data may also be obtained from patient diary cards, but information thus collected must be reviewed and assessed medically before it is transcribed to the CRF.

To elicit adverse events, questioning at each trial visit should begin with simple non-leading questions. For example:

"How have you felt since your last visit?"

"Have you had any health problems since you were here last?"

If a patient is seen by a physician not involved in the trial in relation to an adverse event, the Investigator should make every effort to contact the treating physician in a timely manner in order to obtain all information necessary to appropriate reporting of the event.

12.2.2 Recording Adverse Events

As the quality and precision of acquired AE data are critical, the Investigator should use the adverse event definitions provided in the above sections and should observe the following guidelines when completing the AE pages of the CRF:

- Whenever possible, recognized medical terms should be used to describe AEs rather than colloquialisms (for example, 'influenza' rather than 'flu'), and abbreviations should be avoided.
- Adverse events should be described using a specific clinical diagnosis, if this is available, rather than a list of component signs or symptoms (for example, 'congestive heart failure' rather than 'dyspnea, rales and cyanosis.')
- However, signs and symptoms that are not linked (as "co-manifestations") to an identified disease or syndrome, or for which an overall diagnosis is not available, should be reported as individual AEs.
- Provisional diagnosis (e.g. "suspected myocardial infarction") are acceptable but should be followed up to a definite diagnosis if finally available.
- Adverse events occurring secondary to other events (e.g. sequelae or complications) should be identified by the primary cause. A primary AE, if clearly identifiable, generally

represents the most accurate clinical term to record in the eCRF. The Investigator should be invited to provide his/her opinion of which is the primary AE, or "Reporter's highlighted term".

Complete and accurate data on all AEs experienced for the duration of the reporting period, as defined in section 13.5, will be reported on an ongoing basis in the AE pages of the eCRF.

It is important that each AE report includes a description of the event, whether it is considered serious (and if so the criterion satisfied), its duration (onset and resolution dates), its severity, its relationship to the Investigational Medicinal Product, any other potential causality factors, any treatment given or other action taken (including dose modification or discontinuation of the Investigational Medicinal Product) and its outcome.

12.2.3 Grading of Severity

All adverse events will be classified as

Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the patient is unable to carry out usual activities and/or the patient's life is at risk from the event.

The term "severe" is used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). This has to be clearly distinguished from the term "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations (see section 13.4).

12.2.4 Grading of Relationship to IMP (Causality)

<u>Not assessable:</u>

- Report suggesting an adverse reaction
- Cannot be judged because information is insufficient or contradictory.

<u>Not related</u>

Reports including good reasons that the AE was not related to the investigational product, but was caused by other factors such as the patient's clinical state, therapeutic interventions

or concomitant products administered to the patient and does not follow a known response pattern to the trial medication.

Unlikely

Reports including reasons that the causal relationship to the investigational product cannot be excluded beyond reasonable doubt, but indicating that the AE was more likely caused by other factors such as the patient's clinical state, therapeutic interventions or concomitant products administered to the patient and does not follow a known response pattern to the trial medication.

Possible

Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection may be uncertain or doubtful, for example because of missing data or insufficient evidence.

Probable

Reports including good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable.

Certain:

- Event or laboratory test abnormality, with plausible time relationship to drug intake
- Cannot be explained by disease or other drugs
- Response to withdrawal plausible (pharmacologically, pathologically)
- Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon)
- Rechallenge satisfactory, if necessary

12.3 Expedited Reporting Procedure

Any clinical adverse experience or abnormal laboratory test result that is serious (see 13.1.2), occurring during the course of the trial, irrespective of the treatment received by the patient, must be reported by the Investigator by forwarding a completed "Serious Adverse Event report form" in the respective section of the eCRF immediately after becoming aware of the event, i.e. within 24 hours at the latest. Adverse events that are serious require all of the actions specified for adverse events and, in addition, must be reported immediately., For any new SAE, the following minimum information is required as initial notification:

- Clear identification of the Investigator/Reporter with full contact information

- Patient identification details (trial number, site number, patient identification number, date of birth),
- Investigational Medicinal Product administration details (dose and dates)
- Diagnosis of the event with the description (or a brief description of signs/symptoms/clinical course if the diagnosis is not available) and the date of onset,
- Reason(s) for considering the event serious, and,
- Relationship of the event with the Investigational Medicinal Product or with the trial procedure (e.g., the causality according to the Investigator)

In addition, the Investigator/Reporter must respond to any request for follow-up information or questions the Sponsor may have regarding the AE within the same timelines as for initial reports.

SAEs must be recorded in the AE section of the eCRF within 24 hours. Initial SAE reports must be followed by detailed descriptions which may include copies of hospital case reports, autopsy reports and other documents when requested and applicable. The Investigator must ensure that the patient's anonymity will be maintained. The patient's name must be replaced by the Pat. ID.

For reporting SAEs in the event of technical failure, SAE paper forms need to be faxed within 24 hours using the following contact:

AMS Advanced Medical Services GmbH
Pharmacovigilance Department
SAE-Fax: ++49-(0)621-70095950

Any requested supporting documentation (e.g., discharge summary, ECG, laboratory results, autopsy report) should also be sent to the same adverse event reporting contact.

12.4 Reporting to the Institutional Review Board / Independent Ethics Committee

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of "findings that could affect adversely the safety of patients, impact the conduct of the trial or alter the IRB/IEC's approval/favorable opinion to continue the trial." In particular and in line with respective regulations the Sponsor will inform the Investigator of adverse events that are both serious and unexpected (i.e. unlisted as per IB) and are considered to be possibly or probably related to the administered product by the Investigator/Reporter. The Investigator will confirm receipt of these safety reports and will keep copies of these reports in the Investigator Site File. National regulations with regards to safety reports notifications to investigators will be fully taken into account.

The Sponsor will provide appropriate safety reports directly to the concerned IRB/IEC and maintains records of these notifications.

12.5 Reporting Period

Adverse Events (AEs) are collected on an on-going basis from the day of written informed consent until the last patient visit required by the protocol.

Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them (according to CT-3, 2011/C 172/01: Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use).

In case of on-going SAEs at trial termination, the events should be followed up with reasonable effort until they have been resolved or until the degree of a permanent disability can be assessed. If a patient is documented as lost-to follow-up, on-going/unknown outcome AEs will not be followed-up.

For screening failures, all AEs and updates must be recorded in CRFs until the date the patient was determined to be a screening failure.

AEs that occur during the trial should be treated by established standards of care, which will protect the life, and health of the patient. Supplementary investigations based on the medical judgment may be applied by the investigator.

12.6 Pregnancy and In Utero Drug Exposure

Only pregnancies considered related to trial treatment by the Investigator (i.e. resulting from a drug interaction with a contraceptive medication) are considered as adverse events. However all pregnancies occurring from the date of Informed Consent signature until at least 24 hours after the last Investigational Medicinal Product administration must be recorded by convention in the AE page of the CRF.

In parallel the Investigator must notify the Sponsor in an expedited manner of any pregnancy occurring during the above-mentioned period, by completing Part I of the Pregnancy Report. This form should be sent to the Sponsor as per the same procedures and timelines described for expedited AE reporting in section 13.3.

Investigators must actively follow-up, document and report the outcome of all these pregnancies to the Sponsor, even if the patient was withdrawn from the trial.

Pregnancy outcomes are not recorded in the CRF unless considered adverse events.

Pregnancy outcomes must be reported to the Sponsor by completing Part II of the same Pregnancy Report used for the initial pregnancy notification. Timelines vary according to the nature of the pregnancy outcome:

- For normal outcomes, the Sponsor should be notified within 45 days from birth/delivery.
- For abnormal outcomes, the fully completed form must be sent to the Sponsor according to the same procedures and timelines described for expedited AE reporting in section 13.3. A SAE Report form must be completed when the patient sustains an event while a Parent-Child/Foetus Report (PCFR) must be completed when the child/foetus sustains an event.

13 PATIENT COMPLETION AND WITHDRAWAL

Patients will be informed that they have the right to withdraw from the trial at any time, without prejudice to their medical care, and that they are not obliged to state their reasons. Any withdrawal must be fully documented in the CRF and source documents, and should be followed up by the Investigator.

The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.

13.1 Premature Discontinuation of the Patient

Patients may be withdrawn from the trial by the Investigator for any of the following reasons:

- new occurrence or late evidence of exclusion criteria
- use of prohibited medication
- adverse events, when continuation of treatment would constitute an unacceptable risk for the patient. This includes complications related to trial specific procedures
- relevant protocol violations (e.g. continuously missed evaluations of efficacy variables, major deviations in the dosing schedule or in the timing of efficacy related assessments)
- lack of efficacy
- pregnancy
- patient is not willing or unable to adhere to trial requirements
- circumstances of life that make further participation in the trial impossible, e.g. patient relocation

Patients who miss one visit will not be withdrawn from the trial for this reason.

Patients who discontinue the trial prematurely after having received at least one dose of IMP will be regarded as "drop outs", and the circumstances of their withdrawal or discontinuation must be documented in the CRF. The IMP supplied to these patients must be retrieved completely and may not be redistributed to other patients. If a patient discontinues, a complete final examination as scheduled for the final visit (V15) should be performed.

Withdrawn patients who suffer from an adverse event which has not recovered at the time of the final examination will be followed-up as described in section 12.5.

Patients who terminate the trial prematurely for whatever reason will not be replaced.

Patients who turn out to be unsuited for trial participation during the screening period prior to treatment will be regarded as “screening failures”, and will be replaced.

13.2 Premature Discontinuation of the Trial

The Sponsor reserves the right to prematurely terminate the trial for any reason at any time, after discussion with the Coordinating Investigator.

The Sponsor may terminate the trial if

- drug-related adverse events occur which constitute a serious risk to the health of the participating patients,
- the risk-benefit assessment becomes negative.

In any case of a termination/suspension of the trial the investigators, the Ethical Committees and the regulatory authorities have to be informed promptly of the termination/suspension and of the reason(s).

The Sponsor reserves the right to prematurely terminate the trial in single trial sites if

- the trial sites does not comply with the requirements settled in the trial protocol,
- the trial sites does not adhere to the standards of Good Clinical Practice,
- the time schedule settled for the recruitment of patients is not complied with.

13.3 Planned Treatment after a Patient’s Trial Completion or Withdrawal

After completion of the double-blind treatment phase or in the case of withdrawal due to lack of efficacy, patients may continue treatment with apomorphine during the open label phase after an intermediate wash-out and re-titration phase.

14 BIOMETRICAL METHODS FOR DESIGN AND ANALYSIS

14.1 Test of Hypotheses

The null hypothesis for the analysis is $p_X=p_C$, and the alternative is $p_X \neq p_C$. Where p_X and p_C are the absolute changes in the experimental group (Apomorphine) and the control group (Placebo), respectively.

14.2 Sample Size

Based on previous experience / review of published apomorphine data (Katzenschlager et al., 2005) it is assumed that an OFF-time baseline value of 6.5 hours will be reduced to 3.5 hours under apomorphine and to 5 hours under Placebo. A two-sample t-Test allowing for unequal variances (Standard deviation of 1.75 hours for apomorphine and 2.5 hours for placebo) requires 68 evaluable patients (1:1 treatment balance). Allowing 5% extra for the non-parametric testing 72 evaluable patients are needed. If 30% of the randomized patients are not evaluable for the primary endpoint, a total of 102 patients need to be randomized.

The assumptions of the sample size calculation will be reviewed when about 50% of the patients have been enrolled. Review will be done using the blinded baseline mean/ standard deviation of the OFF times of all randomized patients. It will be checked whether the intended mean OFF of 6.5 hours is within the probable range. In case the mean OFF time duration is not as expected a recalculation of the sample size will be considered.

14.3 Handling of Withdrawals, Protocol Violators and Missing Values

Data from patients who prematurely terminate the trial will be used to the maximum extent possible.

For the primary efficacy endpoint analyses missing values in the patient diaries will be handled as follows. For the calculation of the absolute time spend OFF per day no more than four absent or multiple responses per half-hour period are allowed. If more than four absent or multiple responses occur, this patient diary day will not be included in analysis of the primary endpoint. If a patient drops out of the study the absolute OFF times will be replaced according to the principle of the last observation carried forward (LOCF) - conservative approach.

Other missing values will be replaced according to the principle of the last observation carried forward (LOCF).

Criteria for protocol deviations will be defined and reviewed prior to database lock and described in the SAP. The following protocol deviations will be considered:

- Violation of exclusion or inclusion criteria
- Intake of non-permitted concomitant drugs as listed in the protocol
- Non-compliance to treatment (major deviations from the planned schedule of administration)
- Continuously missed evaluations of efficacy variables or major deviations in the timing of efficacy related assessments

All protocol deviations will be listed and will be assessed as major or minor during a blind data review meeting (BDRM) with regard to their influence on any of the efficacy variables prior to database lock. A major violation may also be a combination of minor deviations.

14.4 Analysis Sets

The assignment of individual patients to the analysis sets will be determined by the Review Committee. The following 4 analysis sets will be identified:

All Patients Set:

This is the group of all patients who signed the informed consent form. Only screening data will be described for this set.

Safety Set:

This set comprises all patients who received at least one dose of treatment. The patients will be analyzed “as treated”.

Full Analysis Set (FAS):

This population includes all randomized patients who received at least one dose of treatment and for whom any efficacy assessment is available. The patients will be analyzed “as randomized” (intention-to-treat principle). This will be the primary population for efficacy analyses.

Per-Protocol Set:

The per-protocol set includes all patients of the full analysis set except patients with major protocol violations and patients not sufficiently treated with (active) treatment. Per protocol analyses will be used for sensitivity analyses.

14.5 Statistical Methods

14.5.1 General Considerations

All variables will be described by treatment group using descriptive statistics.

Summary statistics (n, arithmetic mean, standard deviation, coefficient of variation, minimum, 1st quartile, median, 3rd quartile, and maximum) will be provided for quantitative data, for qualitative data frequency tables will be provided.

All significance tests will be reported on a two-sided significance level of 0.05. Besides the hypothesis testing of the primary variable, all tests are for exploratory use only.

A statistical analysis plan (SAP) will be written in order to describe details of statistical evaluation. This plan will be finalized prior to database lock.

14.5.2 Screening Assessments

All analyses on the screening data will be based on the All Patients Set. The screening parameters will only be listed.

14.5.3 Baseline Assessments

All patient demographic data and baseline characteristics will be listed and tabulated based on the Full Analysis Set, the Per-Protocol Set and the Safety Set.

14.5.4 Efficacy Analysis

Efficacy analyses will primarily be performed for the Full Analysis Set; the Per-Protocol Set will be used to explore the robustness of the findings.

14.5.4.1 Primary Efficacy Analysis

The primary efficacy endpoint is the absolute change in time spent “OFF” from baseline to the end of 12 weeks double-blind treatment period based on patient diaries. The average of the two days prior to baseline and week 12, respectively, will be used to calculate the absolute time spent “OFF”.

A Wilcoxon Rank Sum Test will be used to test the primary hypothesis (superiority of apomorphine vs. placebo). The test shall be performed using a Type I error level of 0.05 two-sided and 80% power.

14.5.4.2 Secondary Efficacy Analysis

The secondary efficacy endpoints are:

- Percentage of patients with response to therapy, defined as an OFF time reduction of at least 2 hours, from baseline to end of 12 weeks double-blind treatment period
- Patient Global Impression of Change
- Absolute change in time spent “ON without troublesome dyskinesia”
- Change in oral L-dopa and L-dopa equivalent dose
- Change in Unified Parkinson’s Disease Rating Scale (UPDRS Part III motor examination) during ON periods
- Change in Quality of Life (using PDQ-8)

For all secondary variables, descriptive statistics comparing the two treatment groups will be performed. Group comparisons of dichotomous variables will be tested using the Fisher’s Exact Test; comparisons of continuous numeric variables are specified by using a Wilcoxon Rank Sum Test.

14.5.4.3 Exploratory Endpoints

The exploratory endpoints are:

- Change in Score of the Non-Motor Symptoms Scale for PD
- Change in MDS-UPDRS Part I patient questionnaire = non-motor experiences of daily living
- Change in MDS-UPDRS II during ON and OFF state
- Change in MDS-UPDRS Part IV fluctuations = 4.3 and 4.4 combined
- Drop-outs due to lack of efficacy
- Beck Depression Scale
- PDSS (PD Sleep Scale)

For all exploratory variables, descriptive statistics comparing the two treatment groups will be performed.

14.5.5 Safety Analysis

All safety analyses will be based on the Safety Set. The safety parameters will be summarized by treatment group.

The safety endpoints are:

- Evaluation of adverse events and local tolerability
- Skin changes
- Full blood count
- Epworth Sleepiness Scale
- QUIP
- C-SSRS

14.5.5.1 Adverse Events

Adverse events will be coded according to MedDRA. Adverse event listings will be provided including MedDRA Low Level Term (LLT) and original verbatim.

The incidence of adverse events will be summarized using MedDRA terms grouped by primary System Organ Class (SOC) and Preferred Term (PT). Separate frequency tables for incidence of adverse events by intensity and for adverse events related to study drug will be presented. The frequency tables will include the number and percentage of patients who experienced adverse events and the number of events.

Deaths, serious adverse events and adverse events leading to study discontinuation will be listed separately.

14.5.5.2 Laboratory Data

Laboratory test results will be listed and summarized by treatment group. Laboratory values outside the normal range will be marked. Clinical significant parameters will be identified.

14.5.5.3 Vital Signs

Vital signs will be listed as actual values and summarized by treatment group.

14.6 Subgroup Analyses

Subgroup analyses may be performed and defined prospectively after the full clean data sets are secured and based on the data structure prior to unblinding.

14.7 Interim Analysis

No unblinded interim analysis is planned.

14.8 Others

Disposition of patients (including reason for any discontinuations) and exposure to study drug will be summarized by treatment group.

15 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

This trial will be performed in accordance with the protocol, the Declaration of Helsinki, the ICH Harmonized Tripartite Guideline for GCP, and all applicable national regulatory requirements.

15.1 Regulatory Authority Approval

Before the trial is initiated, the Sponsor will obtain approval to conduct the trial from the appropriate Competent Authorities in accordance with any applicable country-specific regulatory requirements.

15.2 Institutional Review Board / Independent Ethics Committee Requirements

Before initiation of the trial, written approval of the protocol, Informed Consent form and any information presented to potential patients will be obtained from the appropriate Institutional Review Board or Independent Ethics Committee of each participating country.

15.3 Changes to the Protocol

Protocol modifications which affect the safety of the patients or which alter the scope of the investigation, the scientific quality of the trial, the experimental design, dosages, assessment variable(s), the number of patients treated or the patient selection criteria must be made only after discussion between the Sponsor and the Principal Investigator. Any change to the protocol can only be made in the form of a written amendment to the trial protocol. Such amendments have to be signed by the Sponsor, the Principal Investigator and *AMS* prior to implementation.

If protocol changes are necessary which require the preparation of an amendment, this amendment will also be submitted to the Competent Authorities and relevant ECs in each participating country according to the national requirements, for substantial amendments written approval will be obtained prior to their implementation.

Amendments which might have an impact on the well-being of the patients, such as the use of additional invasive examination methods, have effects on the informed consent procedure and require the signature of the revised informed consent form by all patients enrolled in the trial who are affected by the amendment.

15.4 Notification of Authorities

The participating investigators may have to announce their trial participation to local authorities according to the regulatory requirements of each participating country. If permitted and requested by the Investigator, the announcement can be arranged by the Sponsor.

15.5 Ethical Considerations

The Investigator will assure that the trial will be conducted in accordance with prevailing local laws and that he/she will comply with the provisions as stated in the revised Declaration of Helsinki and ICH-GCP, whichever represents the greater protection of the patient. It is understood that the Investigator accepts and follows all issues of this trial protocol which must be signed by him/her and must be approved by the ethics committee and the competent authority prior to initiation of the trial.

15.6 Patients' Information and Informed Consent

The patient`s information and informed consent forms are to be signed twice: once at entry into the study and again at V11 (prior to any procedures) to confirm willingness to participate in the open-label phase. It is the responsibility of the Investigator to ensure that no patient undergoes any trial related examination or activity before having given written informed consent. Informed consent shall be obtained from the patient him/herself. The Investigator or a physician designated by the Investigator will inform the patients that they are completely free to refuse to enter the trial or to withdraw from it at any time. Subjects who refuse to give written informed consent or withdraw their informed consent later on must not be included in the trial or must be excluded from further participation, respectively. Before personally dating and signing the informed consent form the patients will be informed in detail by the Investigator about all pertinent aspects of the trial according to ICH-GCP.

All patients should be given sufficient time to request further details about the trial before signing the informed consent form, which conforms to the ICH-GCP Guidelines. The receipt of the patient's informed consent must be documented on the appropriate page of the patient's CRF and in the source documents.

One copy of the consent form signed and dated by the patient and by the physician who informed the patient will be kept at the trial site; a second copy will be handed over to the patient. Each patient must receive a patient information sheet written in local language.

15.7 Measures Taken to Prevent Patient Participation in another Trial at the Same Time

Patients will be informed by the Investigator that participation in other clinical trials is prohibited. The exclusion criteria are also re-assessed before randomization and if a patient has entered a different trial at that time, the patient will not be randomized and excluded from this trial.

15.8 Patient Insurance

Insurance coverage shall be provided in accordance with the regulations of each individual country for all patients enrolled in the study from the time of the patient´s inclusion into the study (i.e. from the time informed consent is given). Appropriate insurance coverage is provided by the Sponsor, in line with legal requirements and GCP guidance and in accordance with the (local) regulations of each individual country. Different insurance providers may be required, in accordance with local regulations or service availability.

The Patient Insurance Certificate and the provision clauses will be filed in the Investigator's Site File. Copies will be handed out to the patients if required.

15.9 Confidentiality of Trial Documents and Patient Records

According to ICH guideline "Note for Guidance on Good Clinical Practice" (ICH-GCP) 5.15.2, the Sponsor must "verify that each patient has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection". With this consent the patient also gives his/her agreement to the documentation of clinical data in the bounds of the clinical trial, to their transmission for review to the Sponsor, to the responsible regulatory authorities and, in case of person related data, to their perusal by representatives of the Sponsor or of the authorities.

Neither the names of the patients nor any other records identifying the patients will be made publicly available by the Investigator or by the Sponsor. According to ICH-GCP the patient has to agree with his/her informed consent that representatives of the Sponsor, the regulatory authorities or the Ethical Committees obliged to keep confidentiality are authorized to inspect the patient file or any other source data. This authorization has to be given in writing prior to the beginning of the clinical trial. It is understood that a patient not giving this authorization must not be enrolled in this trial.

The Investigator must ensure that each patient's anonymity will be strictly maintained. On CRFs or other documents submitted to the Sponsor, patients must not be identified by their name, but by an identification code consisting of the Pat. ID. If patient names are included on copies of documents submitted to the Sponsor, the names must be obliterated and the

assigned Pat. ID must be added to the documents instead. The investigator will keep a separate Patient Identification Code List of these codes, along with the full names and dates of birth of the patients. Documents which contain the names associated with these codes are not for submission to the Sponsor. They will, together with completed consent forms, be maintained by the Investigator in strict confidence.

15.10 Monitoring

The Investigator will permit the monitor designated by the Sponsor to monitor the trial according to the relevant SOPs and GCP guidelines. Monitoring visits will be performed as frequently as deemed necessary by the Sponsor to verify the correct entries of data and the conduct of the trial in accordance with the protocol and with regard to factors such as the trial design, frequency of patient visits and site enrolment rate The first monitoring visit will take place within four weeks after randomization of the first patient at a trial site.

The Investigator must ensure that CRFs are completed in a timely manner and must allow the Sponsor's representative (trial monitor) access to CRFs, patient records and all trial-related materials. During each monitoring visit the monitor will check the entries made in the CRFs and compare these entries with the source data, e.g. the patient's medical records or laboratory results (source data verification). For patients who underwent treatment the Pat. ID, randomization number, informed consent, demographic data, inclusion/exclusion criteria, concomitant diseases, concomitant treatment and all adverse events will be verified by 100%.

For all patients who were screened but not enrolled to treatment and discontinued without at least one application of IMP (screening failures) only the Pat. ID, informed consent and demographic data will be verified by 100%.

The monitor will check all data for plausibility and completeness in collaboration with the Investigator. At the same time a data check for medical plausibility and conformity with GCP will be performed.

It is understood that the Investigator and his/her personnel will assist the monitor in every respect and provide them with all relevant trial data.

15.11 Access to Source Data

For every patient, the original patient's file should clearly document at least:

- Last and first name
- Date of birth
- Sex
- Date of the consent form signature
- Date of entry in the trial

- Trial protocol number
- Diagnosis of Parkinson's Disease
- Concomitant diseases and medication taken at entry in the trial
- Date of each trial visit
- Date and time of all trial related measurements
- Date and time of all apomorphine applications
- Adverse events and changes in the concomitant therapy throughout the trial
- End of trial status
- Date of the trial termination (in case of withdrawal the reason must be indicated)
- For patients admitted as day-cases the name of the carer must be documented

The Investigator will permit trial-related monitoring, audits, EC review, and regulatory inspections, providing direct access to all source data/documents. All persons involved are bound to maintain strict confidentiality concerning the identification of the patient.

15.12 Collection of Data, Direct Entry

All data obtained during this clinical trial will be captured electronically in a project specific programmed EDC application. The eCRFs were specifically designed for the collection of the clinical data detailed in this trial protocol.

All data entered into the eCRF will have to be verified by the original patient's file.

For each patient enrolled after allocation of a Patient ID all trial-related visits of the screening period as well as of the treatment and observation period will be recorded in the eCRF. This eCRF must be completed by the Investigator for all patients, whether they completed the trial according to protocol or dropped out prematurely. If a patient withdraws from the trial, the reason must be stated in the eCRF. The documentation in the eCRFs has to be signed off by the investigator electronically.

All paper forms should be completed using a ball-point pen. Corrections must be signed /dated and ensure that original entries are readable.

Prior to the beginning of the trial the Investigator has to establish a list of the individuals with trial-related duties and of the persons authorized to make entries and data changes in the eCRFs. These persons will be listed giving their function in the trial, their full names, initials and signatures and stating the date of the allocation of their duties in the Investigator's Site File.

15.13 Protocol Violations

Protocol violations or deviations are any non-adherences to the procedures outlined in this document and include, but are not limited to, late evidence of exclusion criteria, missed evaluations, incorrect timing of evaluations or dosing and intake of prohibited medication.

After a patient has been enrolled it is the Investigator's responsibility to make any reasonable effort to avoid and/or correct protocol deviations.

During the course of the trial, major protocol violations will be reported to the Sponsor in the monitoring reports. In addition, protocol violations will be listed and the evaluability of the patients concerned will be discussed by a Review Committee prior to the statistical analysis.

In case of any emergency or adverse event that requires a protocol deviation in order to protect the concerned patient from harm, the Investigator should contact the Sponsor as soon as possible to enable a decision whether or not the patient may continue in the trial.

15.14 Quality Assurance of Clinical Trials

This clinical trial will be conducted in accordance with the protocol, the ICH guideline "Note for Guidance on Good Clinical Practice" (ICH-GCP), and the applicable regulatory requirements (ICH-GCP 6.2.5).

The trial will be conducted and reported in concordance with the applicable Standard Operating Procedures (SOPs) of *AMS* GmbH.

For quality assurance reasons the Sponsor, a third party on behalf of the Sponsor, regulatory agencies or IRB/IECs may conduct quality assurance audits at any time during or following a trial. The Investigator must agree to allow auditors direct access to all trial-related documents including source documents, and must agree to allocate his or her time and the time of his or her trial staff to the auditors in order to discuss findings and issues.

Audits shall ensure that the trial is planned, conducted, evaluated and reported in concordance with this protocol, the applicable Standard Operating Procedures (SOPs) of *AMS* GmbH**,** the ethical principles that have their origin in the Declaration of Helsinki, the requirements of the ICH Harmonized Tripartite Guidelines "Note for Guidance on Good Clinical Practice" and "Note for Guidance on Structure and Content of Clinical Study Reports", local drug laws, and other relevant documents, and that the documentation of the trial is available, complete, organized and valid.

15.15 Steering Committee

A Steering Committee will be constituted in order to ensure the appropriate conduct of the trial. Members will include representatives from the study's Sponsor and principal investigators who take scientific leadership of the clinical trial.

15.16 Archiving of Essential Documents by the Investigator

The Investigator has to archive all essential records and documents as specified by ICH-GCP, and for the period determined by applicable regulatory requirements.

According to ICH-GCP, these documents have to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the trial medication.

The Investigator should be informed by the Sponsor when the documents need not to be retained any longer. The Investigator will inform the Sponsor of the storage location of the essential documents, and must contact the Sponsor for approval before disposing of any. The Investigator should take measures to prevent accidental or premature destruction of these documents.

If required, the Sponsor may take over the archiving duties for the Investigator.

15.17 Archiving of Essential Documents by the Sponsor

According to ICH-GCP all relevant forms and essential documents should be available at the Sponsor's site. During the conduct of the trial and until the Clinical Study Report has been finalized, they will be kept by *AMS* in order to compile a complete Trial Master File. Documents concerning the manufacturing of the IMP will be kept at the Sponsor. After finalization of the Clinical Study Report the complete Trial Master File and other essential documents compiled by *AMS* will be forwarded to the Sponsor without retention of any copies.

15.18 Proprietary Rights on Trial Data and Publication of Results

Data and results of this clinical trial are the sole property of the Sponsor and may be used world-wide for product documentation and publications.

By conducting this trial, the Investigator affirms to the Sponsor that he/she will maintain, in strict confidence, information provided to him/her by the Sponsor, including data generated from this trial, except as exempted for regulatory purposes. The Investigator must not submit any results of this trial for publication or presentation without allowing the Sponsor 30 working days in which to review and comment upon the pre-publication manuscript.

All manuscripts, abstracts or other presentation materials generated from trial data will be reviewed and approved by both the Sponsor and the Principal Investigator prior to submission. This will allow the Sponsor to protect proprietary information and enable both

parties to provide comments based upon information that may not yet be available to the other.

In accordance with generally recognized principles of scientific collaboration, co-authorship with any personnel involved in this trial will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

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17 SIGNATURES

The persons signing below agree that this clinical trial will be conducted in compliance with the protocol, the ICH-GCP guidelines and all applicable regulatory requirements.

Coordinating Investigator

Date	Priv.-Doz. Dr. Regina Katzenschlager,

Britannia Pharmaceuticals Ltd

Date Olga Kuehnel, MD, Head of Clinical Services

Quality Management:

Date Craig Stokes, Quality Assurance Manager

Drug Safety:

Date Andreas Iwanowitsch, PhD, Head Global Pharmacovigilance Unit

***AMS* Advanced Medical Services GmbH**

Date	Gabriele Feldmann PhD, Project Manager
Date	Florian Schelz, Statistics and Data Management

I, the undersigned, am responsible for the conduct of this clinical trial at this site and agree to the following:

- I understand and will conduct the trial according to the protocol, any approved protocol amendments, ICH GCP and all applicable regulatory authority requirements and national laws.
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the Institutional Review Board or Independent Ethics Committee, except where necessary to prevent any immediate danger to the patient.
- I have read and fully understand the investigational product information, and I am familiar with the Investigational Medicinal Product(s) and its/their use according to this protocol.
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.
- I will ensure that any staff at my site(s) who are involved in the trial conduct are adequately trained regarding the Investigational Medicinal Product(s), the protocol and their responsibilities. In the case of delegating any of my trial responsibilities I will provide the Sponsor with written documentation of the delegation of activities.
- I understand that all information concerning the Investigational Medicinal Product(s) supplied to me by the Sponsor in connection with this trial and not previously published is considered confidential information. The information includes the clinical protocol, Case Report Form, assay methods, technical methodology and basic scientific data. I agree that documents and other data pertinent to this trial are the property of the Sponsor.

By my signature below, I hereby attest that I have read, understood and agree to abide by all conditions, instructions and restrictions contained in the above protocol.

Investigator

_____	_____	_____
Date	Print Name	Signature