PROTOCOL SP1006 AMENDMENT 3

A REMOTE, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED STUDY OF ROTIGOTINE TRANSDERMAL SYSTEM IN ADOLESCENT SUBJECTS WITH IDIOPATHIC RESTLESS LEGS SYNDROME

PHASE 3

IND Number: 063902

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LIST OF ABBREVIATIONS

AE	adverse event
ANCOVA	analysis of covariance
ADHD	attention deficit hyperactivity disorder
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
CDMS	clinical data management system
CGI	Clinical Global Impressions
CI	confidence interval
CPM	Clinical Project Manager
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DBP	diastolic blood pressure
eCRF	electronic Case Report form
ECG	electrocardiogram
EoM	End of Maintenance
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICD	impulse control disorder
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IMP	investigational medicinal product
IRB	Institutional Review Board
IRLS	International Restless Legs Rating Scale
IRT	interactive response technology
ISF	investigator site file
LOCF	last observation carried forward

LS	least square
MAO	monoamine oxidase
MedDRA	Medical Dictionary for Regulatory Activities
mMIDI	Modified Minnesota Impulsive Disorder Interview
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PK	pharmacokinetic
PLATFORM	Science 37 Platform
PPS	Per Protocol Set
PS	Patient Safety
PT	preferred term
RLS	Restless Legs Syndrome
RLS-QoL	Restless Legs Syndrome-Quality of Life
RLS-6	Restless Legs-6 Rating Scales
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SOP	Standard Operating Procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WMP	Where's My Patch

1 SUMMARY

This is a Phase 3, remote, double-blind, randomized, adaptive, placebo-controlled study of fixed dose administration of rotigotine transdermal system in adolescent subjects, 13 to 17 years of age, with idiopathic Restless Legs Syndrome (RLS). Subjects will be randomized to 1 of 3 treatment groups: placebo, 2mg/24h rotigotine, or 3mg/24h rotigotine.

The total study duration per subject will be up to 24 weeks including a 4-week Screening Period, a 3-week Titration Period, 12-week Maintenance Period, a Taper Period of 4 days (with de-escalation by 1 dose step every 2 days), and a 30-day Safety Follow-Up Period (for subjects not participating in the open-label, long-term follow-up study). The end of the study is defined as the last visit of the last subject in the study.

A total of 138 subjects are planned to be randomized during the study. A single remote site in the USA is planned to be included in the study. This model integrates telemedicine technology into the clinical research process and supports management of research activities, including data collection.

The primary objective of this study is to demonstrate the efficacy of rotigotine against placebo in adolescent subjects with idiopathic RLS over a 12-week Maintenance Period. The secondary objectives are to investigate the efficacy, safety, and tolerability of rotigotine in adolescent subjects.

The co-primary efficacy variables are change from Baseline to the end of the Maintenance Period in International Restless Legs Rating Scale (IRLS) sum score and change from Baseline to the end of the Maintenance Period in Clinical Global Impressions (CGI) Item 1 score.

Other efficacy variables are change from Baseline by visit in IRLS sum score and Restless Legs-6 Rating Scales (RLS-6).

Safety variables are adverse events (AEs), withdrawals due to AEs, physical and neurological examination findings, changes from Baseline in 12-lead electrocardiograms (ECGs), vital signs, laboratory data, hormone status, body weight, height, body mass index (BMI), and Modified Minnesota Impulsive Disorder Interview (mMIDI).

2 INTRODUCTION

Restless Legs Syndrome, also known as Willis-Ekbom disease, is a common pediatric neurologic condition affecting 2% to 4% of school-aged children and adolescents, with about 25% to 50% of pediatric cases having moderate-to-severe symptoms. Restless Legs Syndrome has a significant impact on sleep, mood, cognition, and function, particularly sleep disturbance. Impairment is often manifested in behavioral and educational domains (Pichietti et al, 2013). Genetic factors, dopamine dysfunction, and low-iron stores may play a role in the pathophysiology of RLS (Simakajornboon et al, 2009). Current evidence supports relative iron deficiency and renal failure as potential aggravating factors for pediatric RLS. Periodic limb movements in sleep and a family history of RLS among first-degree relatives are supportive of pediatric RLS (Pichietti et al, 2013).

The pediatric RLS diagnostic criteria were published in 2003 based on the consensus at a National Institutes of Health workshop (2002) sponsored in part by the International RLS Study Group. These diagnostic criteria were updated in 2013 by the International RLS Study Group

(Picchietti et al, 2013). Ruling out RLS mimics was integrated as an essential element for RLS diagnosis.

Dopaminergic agents are the first-choice treatment for RLS in adults; however, to date, no treatment for RLS has been approved for children. Small published reports suggest that dopamine agonists are effective in the management of RLS in children (Simakajornboon et al, 2009; Cortese et al, 2009; Muhle et al, 2008; Mohri et al, 2008; Konofal et al, 2005; Guilleminault et al, 2003).

The investigational medicinal product (IMP) is a transdermal formulation of the dopamine agonist rotigotine. The patch is applied to the skin and provides constant plasma concentrations. It was first approved by the European regulatory authorities for use in patients with Parkinson's disease in March 2006, and by the US Food and Drug Administration (FDA) in May 2007. Rotigotine transdermal system was approved by the FDA as a treatment for adult patients with RLS in April 2012.

The tolerability of rotigotine transdermal system appears to be within the range of what is known and expected from other dopamine agonists, except for application site reactions, which appear to be mild to moderate in the majority of cases (Perez-Lloret et al, 2013).

UCB has completed a Phase 2 pharmacokinetic (PK)/pharmacodynamic (PD) study in adolescent subjects 13 to 17 years of age, which showed a PK profile similar to that in adult subjects. Although the study was open-label and the sample size was small, the efficacy of rotigotine transdermal system in adolescent subjects also appeared similar to efficacy in adults. Improvements were observed in most efficacy parameters, including the IRLS, CGI Items 1 through 3, and RLS-6, indicating improvements in RLS symptoms and sleep. The purpose of this study is to further investigate the efficacy, safety, and tolerability of rotigotine in adolescent subjects 13 to 17 years of age.

A remote study model will be used to conduct this study. This model integrates telemedicine technology into the clinical research process and supports management of research activities, including data collection. As part of this model, study visits are completed using the unique technology platform called Science 37 Platform, or PLATFORM, which is the backbone of the studies conducted via this model. PLATFORM is the software interface that connects subjects/legal representatives to their investigators/study teams through a study-issued smartphone. This technology will be used in combination with visits from mobile study personnel to subjects'/legal representatives' homes.

3 STUDY OBJECTIVES

The primary objective of this study is to demonstrate the efficacy of rotigotine against placebo in adolescent subjects with idiopathic RLS over a 12-week Maintenance Period. The secondary objectives are to investigate the safety and tolerability of rotigotine in adolescent subjects with idiopathic RLS.

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The co-primary efficacy variables are change from Baseline to the end of the Maintenance Period in IRLS sum score and change from Baseline in CGI Item 1 to the end of the Maintenance Period.

4.1.2 Secondary efficacy variables

Secondary efficacy variables include:

- Change from Baseline in RLS-6 Rating Scales to the end of the Maintenance Period

4.1.3 Other efficacy variables

- Change from Baseline in CGI Item 1 by visit*
- Change from Baseline in RLS-6 Rating Scales by visit*
- Change from Baseline in IRLS sum score by visit*
- IRLS Responder: A responder is defined as a subject with a decrease of ≥50% in IRLS sum score from Baseline
- IRLS Remitter: Two definitions for IRLS remitter will be used in the study; a remitter is defined as a subject with an IRLS sum score ≤10 points or a subject who is symptom free (ie, IRLS sum score of 0 points)
- CGI Item 1 Responder: A responder is defined as a subject with a decrease of ≥50% in CGI Item 1

*For the IRLS, CGI, and RLS-6, the End of Maintenance (EoM) Visit is already covered under primary and secondary variables.

4.2 Safety variables

4.2.1 Primary safety variables

- Occurrence of TEAEs
- TEAEs leading to withdrawals

4.2.2 Other safety variables

- Changes from Baseline (Visit 1) in 12-lead ECGs
- Changes from Baseline (Visit 1) in vital signs (including assessment of orthostasis)
- Changes from Baseline (Visit 1) in laboratory data (hematology, blood chemistry, and urinalysis)
- Changes from Baseline (Visit 1) in hormone status
- Changes from Baseline (Visit 1) in body weight, height, and BMI
- Changes in mMIDI

- Changes in menstrual function for all female subjects

4.3 Other variables

Other variables include:

- Plasma concentrations of unconjugated rotigotine
- Subject Quality of Life Questionnaire

5 STUDY DESIGN

5.1 Study description

This is a Phase 3, remote, double-blind, randomized, adaptive placebo-controlled study of fixed dose administration of the rotigotine transdermal system. The study will be conducted in adolescent subjects, 13 to17 years of age, with idiopathic RLS. Subjects will be randomized to 1 of 3 treatment groups: placebo, 2mg/24h rotigotine, or 3mg/24h rotigotine.

The study will be conducted using the remote study model, which uses telemedicine technology (ie, PLATFORM, see Section 2 for an overview) for interactions between the investigator/study staff and study subjects/legal representatives. Mobile study personnel will visit subjects'/legal representatives' homes to complete certain study procedures (eg, neurological exams, physical exams, ECGs, lab collections, and vital signs).

The study will also utilize a reminder app to help maximize retention of study subjects and limit dropouts. The app, located on the study smartphone, called Where's My Patch (WMP) will help encourage subject adherence to study medication administration by reminding them to place patches at their prespecified time each day. It also provides a body map to record daily patch locations as a visual reminder of where patches have already been placed over the past 14 days and to facilitate patch site rotation. Patch location data will only be retained locally on the smartphone and then automatically deleted after 14 days. Subject use of the MWP app will be encouraged, but not required.

The study will begin with a Screening Period of at least 7 days (maximum of 28 days) prior to Visit 2/Baseline to ensure homogeneous baseline conditions can be established for all subjects. Subjects with prior intake of any dopamine agonists or taking L-dopa must discontinue the therapy at least 7 days prior to Visit 2/Baseline. Discontinuation of therapy must be driven by the subject's medical need and not undertaken for the purpose of making a potential subject eligible for the study.

The Screening Period will be followed by the Titration Period. Subjects will receive their first dose of study medication at Visit 3/Day 1. Subjects will be initiated either on placebo or 1mg/24h rotigotine. The dose of rotigotine taken by subjects randomized to rotigotine will then be up-titrated on a weekly basis by 1mg/24h at a time to 2mg/24h or 3mg/24h, depending on the subject's assigned dose level.

Subjects will be administered study medication according to the dose titration schedule in Section 7.2.1.

Subjects will be allowed to back-titrate 1 dose level during the Titration Period. Subjects are to complete the Titration Period at the back-titrated dose level and remain at this dose level for the duration of the Maintenance Period. If AEs occur during the Titration Period that are thought to

be the result of excessive dopaminergic stimulation (eg, intolerable nausea/vomiting), subjects should be back-titrated to their previous dose level and commence the Maintenance Period immediately. Subjects who do not tolerate the assigned dose in the first week (placebo or 1mg/24h) will be withdrawn from the study. If subjects withdraw due to lack of efficacy, they are eligible to roll over to the open-label study, RL0007, after the 3 weeks of the Titration Period are completed.

The Titration Period will be followed by a 12-week Maintenance Period. Subjects will remain at the assigned (or back-titrated) dose level throughout the Maintenance Period. At the end of the Maintenance Period, subjects will enter a Taper Period lasting up to a maximum of 4 days (de-escalation of study medication), followed by a 30-day Safety Follow-Up Period.

Visits will be scheduled every week during the Titration Period. During the Maintenance Period, visits will be scheduled every 4 weeks. There is a 4-day interval until the end of the Taper Period, followed by a 30-day interval (±5 days) until the Safety Follow-Up Visit. Details are provided in the schedule of study assessments in Section 5.2.

Plasma concentration of unconjugated rotigotine will be summarized by dose levels and visit. Plasma samples will be collected at Visit 6 and Visit 9.

An interim analysis for futility (for the primary outcome measures only), with the possibility of stopping the study early, stopping a dose arm, or continuing the study as planned, will be performed with approximately 33% of the planned number of evaluable subjects; recruitment will not be stopped for the interim analysis. The futility criteria are defined in Section 13.7.

An overview of the study activities is given in Table 5–1 and Figure 5–1.

5.1.1 Study duration per subject

The total study duration per subject will be up to 24 weeks, including a 4-week Screening Period, a 3-week Titration Period, a 12-week Maintenance Period, a Taper Period of 4 days (with de-escalation by 1 dose step every 2 days), and a 30-day Safety Follow-Up Period (for subjects not participating in the open-label, long-term follow-up study).

The end of the study is defined as the last visit of the last subject in the study.

5.1.2 Planned number of subjects and sites

A total of 138 subjects are planned to be randomized during the study. A remote clinical study model in the USA is planned to be utilized in the study.

5.1.3 Anticipated regions and country

This study will be conducted in the USA.

5.2 Schedule of study assessments

The schedule of study assessments is provided in Table 5–1.

Table 5–1: Schedule of assessments

	Screening Period (+1 day)	Rand (+3 days)	Titration Period[a] (±1 day)			EOT/ SOM	Maintenance Period[a] (±2 days)		Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls								Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
Assessment	Day -28 to Day -1	Day 0	Day 1	Day 8	Day 15	Day 22	Day 50	Day 78	Day 106	Day 110		
Informed consent	X											
Demography	X											
Eligibility criteria	X	X										
Withdrawal criteria		X	X	X	X	X	X	X	X			X
Randomization		X										
General medical/ procedures history	X											
Lifestyle	X											
Reproductive potential and birth control	X											
Brief physical examination	X								X		X	X
Neurological examination	X								X		X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X[c]
Vital signs	X					X			X		X	X
Body weight, height, and BMI	X					X			X		X	
12-lead ECG	X								X		X	X
Safety laboratory tests	X					X			X		X	X
Urine drug screen	X											X
Pregnancy Test[d] (hCG)	X					X			X		X	X

Table 5–1: Schedule of assessments

	Screening Period (+1 day)	Rand (+3 days)	Titration Period[a] (±1 day)			EOT/ SOM	Maintenance Period[a] (±2 days)		Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls								Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
Assessment	**Day -28 to Day -1**	**Day 0**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 50**	**Day 78**	**Day 106**	**Day 110**		
Hormone status	X								X		X	X
PK sampling[e]						X			X			
IRLS	X	X[f]				X	X	X	X			
CGI	X	X				X	X	X	X			
RLS-6		X				X	X	X	X			
mMIDI	X					X			X			X
Menstrual function[d]		X				X			X		X	X
Subject Quality of Life Questionnaire		X				X			X			
Recording of medication and procedures	X	X		X	X	X	X	X	X		X	X
Adverse event assessment	X	X		X	X	X	X	X	X	X	X	X
Contact IRT	X	X				X	X	X	X		X	X
Dispense study medication			X[g]			X[g]	X[g]	X[g]	X[g]			X
Return unused study medication						X	X	X	X		X	X

Table 5–1: Schedule of assessments

	Screening Period (+1 day)	Rand (+3 days)	Titration Period[a] (±1 day)			EOT/ SOM	Maintenance Period[a] (±2 days)		Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls								Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
Assessment	Day -28 to Day -1	Day 0	Day 1	Day 8	Day 15	Day 22	Day 50	Day 78	Day 106	Day 110		

BL=Baseline; BMI=body mass index; CGI=Clinical Global Impressions; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic Case Report form; EOT=End of Titration; hCG=human chorionic gonadotropin; IRLS=International Restless Legs Scale; IRT=interactive response technology; mMIDI=Modified Minnesota Impulsive Disorder Interview; PK=pharmacokinetic; Rand=randomization; RLS=Restless Legs Syndrome; SOM=Start of Maintenance; V=Visit; WD=withdrawal

Note: The date of informed consent may be prior to screening assessments and study procedures.

Note: Rescreening is allowed with the permission of the Study Physician or representative.

Note: For Visit 2, there is a visit window of +3 days to allow for direct-to-subject shipment of study medication. Visit 3/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 3/Day 1.

Note: Visit 6 is the end of the Titration Period and start of the Maintenance Period. Visit 9 is the end of the Maintenance Period and start of the Taper Period.

Note: All visits are via telemedicine calls, with the exception of Visit 1, Visit 6, Visit 9, and SFU. Unscheduled visits are at the discretion of the investigator and may be telemedicine calls.

[a] The visit window for Titration Visits is ±1 day per visit relative to Visit 3 (day of first dose). The visit window for visits during the Maintenance Period, including the End of Maintenance Visit, is ±2 days per visit. The Taper Period, which will last up to a maximum of 4 days, will start on the day after the End of Maintenance Visit. The visit window for Safety Follow-Up Period is 30 days±5 days relative to the end of the Taper Period. Following dose de-escalation, subjects may be eligible to participate in the open-label, long-term follow-up study (RL0007) at any time prior to the Safety Follow-Up Visit (see Section 5). The Safety Follow-Up Visit is for subjects not entering RL0007.

[b] Assessments to be performed are at the investigator's discretion.

[c] C-SSRS is required if the Unscheduled Visit is conducted due to safety or efficacy reasons.

[d] Pregnancy test and menstrual function for all female subjects; serum pregnancy test at Screening and urine pregnancy test at all other visits. A positive urine pregnancy test must be confirmed by a serum pregnancy test.

[e] At the time of PK sampling, sampling time, time of application of study medication, and application site of study medication should be recorded in the eCRF.

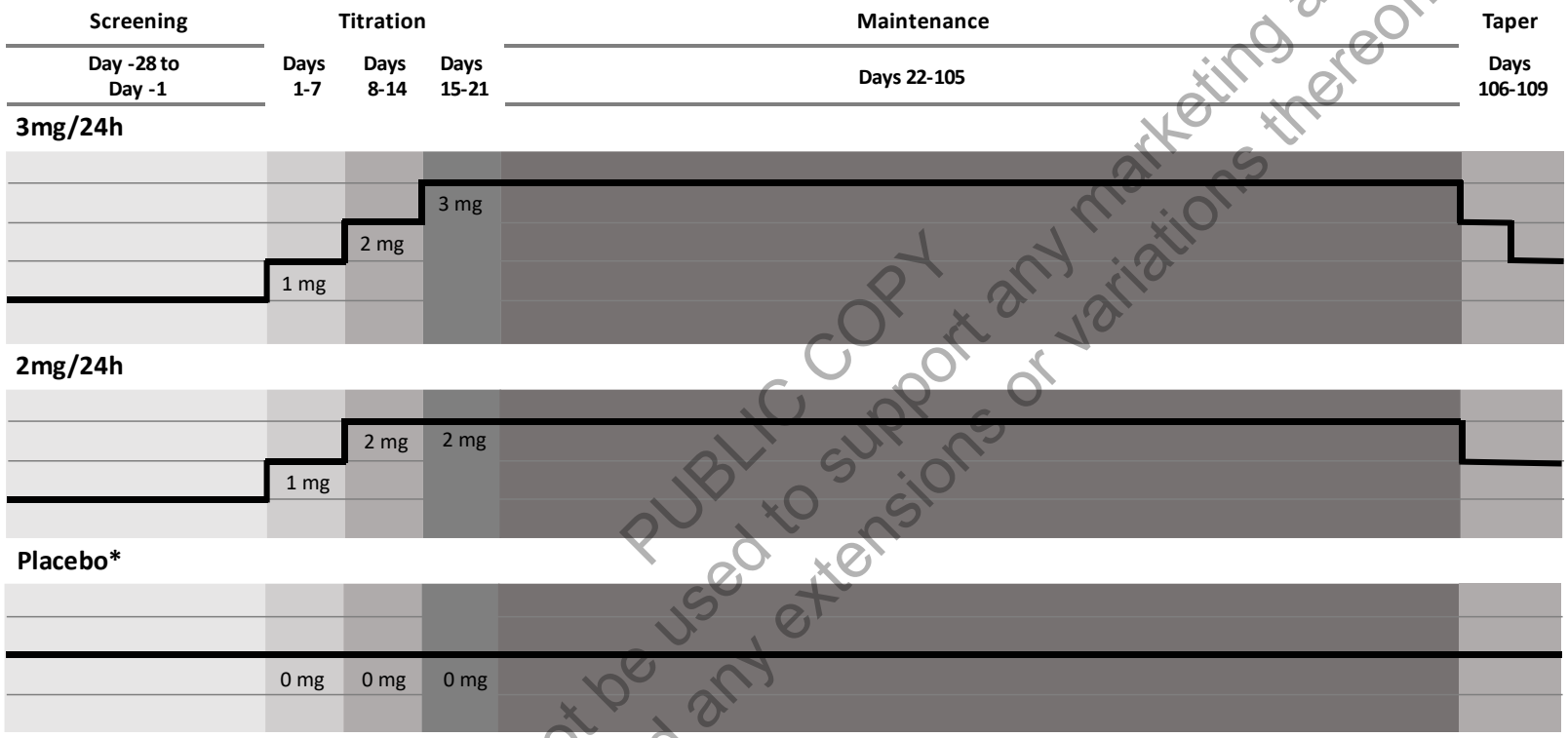
[f] At Baseline, subjects must score ≥15 on the IRLS Rating Scale (indicating moderate-to-severe RLS) and must score ≥4 points on the CGI Item 1.

[g] Study medication to be shipped to subject's home to be available no later than this date.

5.3 Schematic diagram

Subjects will be randomized to 1 of 3 treatment groups:

Figure 5–1: Schematic diagram



* Two patch sizes will be used: 5cm^2 and 10cm^2. Placebo patches will be identical in size and appearance to active patches.

- Subjects will remain at the assigned dose level throughout the 12-week Maintenance Period.
- Subjects will be allowed to back-titrate 1 dose level during the Titration Period. See Section 5.1.
- Subjects will complete the Titration Period at the back-titrated dose level and remain at this dose level for the duration of the Maintenance Period.

5.4 Rationale for study design and selection of dose

SP1006 is a Phase 3, remote, double-blind, randomized, placebo-controlled study of fixed dose administration of the rotigotine transdermal system, designed to investigate the efficacy, safety, and tolerability of rotigotine in adolescent subjects 13 to 17 years of age. The study design is based on the FDA's request to conduct a study in adolescents with RLS. The fixed dose levels of 2mg/24h and 3mg/24h were chosen based on the results of the SP1004 PK/PD study in a similar population.

The PK results of SP1004 were similar compared with those obtained in adults. Rotigotine plasma clearance was similar as compared to adults, although the mean value appeared to be somewhat higher; however, given the high variability, the meaning of this is negligible. Mean volume of distribution, AUC, and C_{max} were similar to results obtained in adults earlier.

In terms of safety, the rotigotine transdermal system was well tolerated at doses of up to 3mg/24h in adolescent subjects with idiopathic RLS. No safety issues were identified in SP1004. A similar number of subjects reported treatment-emergent adverse events (TEAEs) in the 0.5mg/24h, 1mg/24h, and 2mg/24h dose steps during the study, with fewer subjects reporting TEAEs in the 3mg/24h dose step. Overall, 62.5% reported TEAEs, and 45.8% reported drug-related TEAEs. The most frequently reported TEAEs (and drug-related TEAEs) were in the system organ class (SOC) of Gastrointestinal disorders, with nausea the most frequently reported TEAE by preferred term (PT). All of the TEAEs in this study were mild or moderate in intensity. No deaths, serious adverse events (SAEs), or TEAEs leading to discontinuation were reported during the study.

Fourteen subjects from SP1004 were rolled over to open-label extension study SP1005 and were treated for up to 2 years. Overall, rotigotine was well tolerated with long-term use.

Augmentation, defined as an increase in the severity of symptoms beyond baseline levels, represents the main complication of long-term dopaminergic treatment. Augmentation did not occur in SP1004; however, the study was too short to trigger augmentation with less than 5 weeks of treatment in total.

The 2mg/24h and 3mg/24h rotigotine doses chosen for testing in this protocol, SP1006, were selected by balancing the potential need for higher doses with the risk of augmentation as seen in adults receiving doses higher than 3mg/24h. Previous studies have indicated that the incidence of augmentation with rotigotine is low during 6 months and 1 year of treatment. Following an open-label extension study of the long-term safety and efficacy of rotigotine transdermal patch in adult patients with moderate-to-severe idiopathic RLS, a retrospective systematic analysis was conducted in order to investigate the 5-year incidence of augmentation. In this study, the dose was titrated in weekly increments (up to 4 weeks) from 0.5mg/24h to a maximum of 4mg/24h, followed by up to 5 years of maintenance at the optimum dose. Clinically significant augmentation was recorded in 8% of adult patients receiving rotigotine at doses of 4mg/24h compared with 5% of patients receiving rotigotine doses of ≤3mg/24h (Oertel et al, 2011).

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or by the parent(s) or legal representative. The Informed Consent form or a specific Assent form, where required, will be signed and dated by minors.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete questionnaires), visit schedule, and medication intake according to the judgment of the investigator.
3. Subject is male or female, and is ≥13 and <18 years of age at Baseline.
4. Subject weighs ≥40kg.
5. Deleted.
6. Subject meets the diagnosis of RLS based on all of the following features according to the 2013 Revised International RLS Group Diagnostic Criteria (Pichietti et al, 2013):
   - An urge to move the legs usually, but not always, accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs (sometimes the urge to move the legs is present without the uncomfortable sensations and sometimes the arms or other parts of the body are involved in addition to the legs. For children, the description of these symptoms should be in the child's own words.).
   - The urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
   - The urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues (when symptoms are very severe, relief by activity may not be noticeable but must have been previously present).
   - The urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day (when symptoms are very severe, the worsening at night may not be noticeable but must have been previously present).
   - The occurrence of the above features is not solely accounted for as symptoms primary to another medical or behavioral condition (eg, myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping).
7. Subject's RLS symptoms cause significant daytime symptoms or significant distress or impairment in social, occupational, educational, or other important areas of functioning by the impact on sleep, energy/vitality, daily activities, behavior, cognition or mood.
8. At Baseline, subject has a score of ≥15 on the IRLS Rating Scale (indicating moderate-to-severe RLS).
9. At Baseline, subject scores ≥4 points on the CGI Item 1 assessment (indicating at least moderately ill).

10a. Subjects who are receiving supplemental iron have been on a stable dose for at least 1 month prior to Screening. Subjects previously treated with supplemental iron must have a

washout period of at least 1 month prior to Screening. No supplemental iron administration or iron dose adjustment will be allowed while in study, unless medically necessary.

11. Female subjects must be surgically incapable of childbearing, or effectively practicing an acceptable method of contraception (oral/parenteral/implantable hormonal contraceptives, intrauterine device, or barrier and spermicide). Abstinence is an acceptable method. Subjects must agree to use adequate contraception during the study and for 4 weeks after their final dose of study medication.

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Subject has previously participated in this study or subject has received previous treatment with rotigotine.
2. Subject has participated in another study of an IMP or a medical device within the last 3 months prior to Visit 1/Screening or is currently participating in another study of an IMP or a medical device.
3. Subject has clinically relevant renal dysfunction (serum creatinine >1.5mg/dL) at Visit 1/Screening.

4a. Subject has a serum ferritin level below the lower limit of normal at Visit 1/Screening.

5. Subject has a hemoglobin level below the lower limit of normal at Visit 1/Screening.
6. Subject has had previous treatment with dopamine agonists or L-dopa within 7 days prior to Visit 2/Baseline.
7. Subject has any medical or psychiatric condition, which in the opinion of the investigator, would jeopardize or compromise the subject's well-being or ability to participate in this study.
8. Subject is pregnant or nursing.
9. Subject is not willing to abstain from caffeine after 4pm each evening within 7 days prior to Visit 2/Baseline and for the duration of the study.
10. Subject has a QTc interval of ≥500ms at Visit 1/Screening. Bazett's correction method must be used for the correction of the QT interval.
11. At Visit 1/Screening, subject has symptomatic orthostatic hypotension with a decrease of blood pressure (BP) from supine to standing position of ≥20mmHg in systolic blood pressure (SBP) or of ≥10mmHg in diastolic blood pressure (DBP) taken from the 5 minute supine and 1 and/or 3 minute standing measurements.
12. Subject has a known hypersensitivity to any of the components of the study medication, such as a history of significant skin hypersensitivity to adhesives, known hypersensitivity to other transdermal medications or has unresolved contact dermatitis or eczema.
13. Subject has secondary RLS (eg, due to renal insufficiency [uremia], iron deficiency, or rheumatoid arthritis).

14. Subject has a lifetime history of suicide attempts (including actual attempt, interrupted attempt, or aborted attempt), or had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS at Screening (Visit 1).
15. Subject is taking a prohibited concomitant medication (see Section 7.8.2). Prohibited concomitant medication must have been discontinued at least 2 weeks prior to Screening (Visit 1).

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects should be withdrawn from the study if any of the following events occur:

1. Subject develops a physical or mental illness or AE that would interfere with his/her continued participation.
2. Subject is noncompliant with the study procedures or medications in the opinion of the investigator.
3. The investigator feels that it is in the subject's best interest to withdraw from the study.
4. Subject is unwilling to manage the application and removal of patches at any time during the study.
5. The subject develops clinically relevant symptomatic orthostatic hypotension.
6. The subject develops a clinically relevant ECG abnormality that is confirmed by a repeat ECG performed at least 1 hour later. If abnormalities are still present, the subject is to be withdrawn from the study.
7. The subject has a QTc interval ≥500ms and/or a QTc interval which has increased by ≥60ms as compared to the QTc interval taken at Visit 1/Screening. Bazett's method must be used for correction of QT intervals.
8. Subject or parent(s)/legal representative withdraws his or her consent.
9. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
10. The sponsor or a regulatory agency requests withdrawal of the subject.
11. Subject has active suicidal ideation as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Since Last Visit" version of the C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

Investigators/designated study staff should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow up, the investigator/designated study staff should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the

reason(s) for removing the subject, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥ 5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP:

- Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 11.6.1.2 are followed.

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 11.6.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

Table 7–1 provides summary information regarding the products that will be used in this study.

Table 7–1: Investigational medicinal product

International Non-Proprietary Name	Rotigotine	
Dosage form	Silicone patch containing rotigotine in an adhesive matrix	
Content	Nominal Dose (mg/24h)	Patch size (cm^2)
	1	5
	2	10

Placebo patches do not contain drug, but are identical in size and appearance to rotigotine patches.

7.2 Treatments to be administered

7.2.1 Titration Period

The study will begin with a 3-week Titration Period, during which subjects will receive rotigotine patches in escalating weekly doses (from 1mg/24h to 2mg/24h for subjects randomized to 2mg/24h and from 1mg/24h to 2mg/24h to 3mg/24h for subjects randomized to 3mg/24h) until the randomized dose level (or matching placebo) is achieved (Table 7–2). During the Maintenance Period, the subject will continue as per the assigned treatment arm. Following the Maintenance Period, subjects will be de-escalated over 4 days.

Table 7–2: Dose titration schedule

	Rotigotine Nominal Dose (mg/24h)	Patch surface area (cm^2)
Week 1 (Days 1 to 7)	1	1 x 5cm^2 Active OR 1 x 5cm^2 Placebo
Week 2 (Days 8 to 14)	2	1 x 10cm^2 Active OR 1 x 10cm^2 Placebo
Week 3 (Days 15 to 21)	3	1 x 5cm^2 Placebo + 1 x 10cm^2 Active OR 1 x 5cm^2 Active + 1 x 10cm^2 Active OR 1 x 5cm^2 Placebo + 1 x 10cm^2 Placebo

Subjects will be allowed to back-titrate 1 dose level during the Titration Period. Subjects are to complete the Titration Period at the back-titrated dose level and remain at this dose level for the

duration of the Maintenance Period. If AEs occur during the Titration Period that are thought to be the result of excessive dopaminergic stimulation (eg, intolerable nausea/vomiting), subjects should be back-titrated to their previous dose level and commence the Maintenance Period immediately. Visits will be scheduled every week during the Titration Period. If subjects withdraw due to lack of efficacy, they are eligible to roll over to the open-label study, RL0007, after the 3 weeks of the Titration Period are completed.

7.2.1.1 Maintenance Period

The Titration Period will be followed by a 12-week Maintenance Period. Subjects will maintain doses achieved at Visit 6 (end of the Titration Period) throughout the Maintenance Period. During the Maintenance Period, visits will be scheduled every 4 weeks for 3 visits.

7.2.1.2 Taper Period

At the end of the Maintenance Period, subjects will enter a Taper Period lasting up to a maximum of 4 days (de-escalation of study medication) (Table 7–3). Subjects in the 2mg/24h arm and the 3mg/24h arm will taper down to 1mg/24h by the end of the Taper Period. Subjects in the placebo arm will continue placebo throughout the 4-day Taper Period. At the end of the Taper Period, subjects will be contacted by telemedicine call.

Table 7–3: Dose down titration schedule

Rotigotine nominal dose (mg/24h)	Days	Patch surface area (cm^2)
Placebo	107 and 108	1 x $5cm^2$ Placebo + 1 x $10cm^2$ Placebo
	109 and 110	1 x $5cm^2$ Placebo + 1 x $10cm^2$ Placebo
1	107 and 108	1 x $5cm^2$ Active + 1 x $10cm^2$ Placebo
	109 and 110	1 x $5cm^2$ Active + 1 x $10cm^2$ Placebo
2	107 and 108	1 x $5cm^2$ Active + 1 x $10cm^2$ Placebo
	109 and 110	1 x $5cm^2$ Active + 1 x $10cm^2$ Placebo
3	107 and 108	1 x $5cm^2$ Placebo + 1 x $10cm^2$ Active
	109 and 110	1 x $5cm^2$ Active + 1 x $10cm^2$ Placebo

7.2.1.3 Safety Follow-Up Period

The Taper Period is followed by a 30-day interval (±5 days) until the Safety Follow-Up Visit. Details are provided in the schedule of study assessments in Section 5.2.

7.2.2 Application instructions

Following are instructions for patch application:

- The patch should be applied immediately after removing it from the protective pouch.
- Subjects, with the assistance of a legal representative (ie, parent/guardian) as needed, should apply the patch at approximately the same time each day.

- The patch should be worn continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately. The WMP app on the study smartphone provides a reminder to place patches at a subject's prespecified time each day (see Section 5 for an overview).
- The patch should be applied to an area of clean, dry, and healthy skin on the stomach, thigh, hip, flank (side of the body between the ribs and the pelvis), shoulder, or upper arm.
- Each patch should be applied to a different place on the skin each day, for example, from the right side to the left side and from the upper body to the lower body. The patch should not be applied to the same application site more than once every 14 days. The WMP app on the study smartphone provides a body map to record daily patch location and a visual reminder of where patches have been placed over the past 14 days (see Section 5 for an overview).
- When applied, the patch should be pressed firmly into place with the palm of the hand for 30 seconds to make sure there is good contact with the skin, especially around the edges.
- If it is necessary to apply the patch to a hairy area, the area should be clipped at least 3 days prior to applying the patch.
- The patch should not be applied to areas where it could be rubbed by tight clothing or under a waistband.
- Avoid applying the patch on skin folds or body areas of increased sweating.
- Do not apply the patch to skin that is red, irritated, or injured.
- Creams, lotions, ointments, oils, and powders should not be applied to the skin area where the patch will be placed.
- Subjects and legal representatives (ie, parents/guardians) should wash their hands with soap and water immediately after handling the patch.

7.2.3 Removal instructions

Following are instructions for patch removal:

- Slowly and carefully peel off the used patch which still contains some of the drug.
- Carefully fold it in half (sticky sides together) and throw it in the trash.
- Gently wash the area with warm water and mild soap to remove any adhesive that stays on the skin. Baby oil may also be used to remove any excess residue. Alcohol or other solvents, such as nail polish remover, may cause skin irritation and should not be used.
- Subjects may see mild redness at the site when a patch is removed. This redness should disappear over time. If uncomfortable irritation or excessive itchiness continues, subjects and/or their parent/guardian should tell their investigator.

7.2.4 General instructions

Following are general instructions:

- Contact with water while bathing, showering, swimming will not change the way that rotigotine works; however, these activities could loosen the patch. If a patch falls off,

re-apply a new patch for the remainder of the day. A new patch should be applied the next day on the subject's regular schedule. The location of a replacement patch can be recorded in the WMP app on the study smartphone (see Section 5 for an overview).

- If the subject forgets to apply a patch at the usual time, the subject should remove the patch he/she is currently wearing and put a new patch on a different area of skin. Then apply a new patch the next day on the subject's regular schedule.
- Avoid applying heating pads or other sources of external heat to the patch. Avoid exposing the patch to direct sunlight.
- If the subject develops a skin rash or irritation from the patch, avoid direct sunlight on the area until the skin heals because this exposure could lead to changes of skin color.
- Subjects should not reduce the dosage or stop applying a patch without first talking with their investigator.
- Do not cut or damage the patch.
- After 24 hours, the patches should be removed and new ones applied right away to a different area of skin.
- To avoid potential burns, the patch should be removed before undergoing cardioversion or a diagnostic procedure known as magnetic resonance imaging.
- The patches should be stored according to the labeling on the clinical trial supply packaging. Do not store the patch outside pouch.

7.3 Packaging

The IMP will be packaged and labeled by UCB according to current Good Manufacturing Practice (GMP) guidelines and the applicable laws and guidelines. The sponsor will provide site boxes containing complete study medication. The site boxes will be packaged in such a way as to protect the product from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

Rotigotine transdermal patches should be stored in the original pouch. Rotigotine should be stored according to the labeling on the clinical trial supply packaging. The investigator (or designee) is responsible for the safe and proper storage of rotigotine at the site. Rotigotine stored by the investigator (or designee) is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

Appropriate storage conditions must be ensured either by controlled room temperature or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately communicated to the Sponsor's designee in accordance with the Pharmacy Manual. The investigator (or designee) will instruct the subject to store the IMP following the instructions on the label. Detailed information on handling the IMP will be given in the Pharmacy Manual.

As part of the remote study model, the study site's depot/pharmacy will provide study medication and all required supplies via direct-to-subject shipments. Once eligibility is confirmed, the study site will contact the interactive response technology (IRT) for randomization assignment, and shipments will be prepared and sent out for delivery to the subject's/legal representative's home/preferred address. Shipments will be confirmed as delivered by the study staff, with appropriate documentation in the subject's study records. The study medication will be confirmed as received in good condition and within the acceptable temperature range (ie, fit for use). A telemedicine call will be completed to instruct the subject/legal representative on the correct storage and administration of the study medication, which will also be documented as part of subject's study record.

7.6 Drug accountability

At the designated timepoints during the study, subjects/legal representatives will return to the study site's depot/pharmacy the unused study medication patches remaining as part of the medication kits, along with the kit itself, via the return shipment materials provided. A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, disposed of at the study site's depot/pharmacy, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and drug accountability documentation must be made available throughout the study for UCB (or designee) to review.

The investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The investigator may assign some of the investigator's duties for drug accountability at the study site's depot/pharmacy to an appropriate designee.

The investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original package. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

At the designated visits (see Table 5–1), subjects/legal representatives will return all unused IMP and empty IMP containers, using the return shipment supplies provided to them by the study staff. Upon receipt of the returned medication at the study site's depot/pharmacy, the designated study staff will review drug accountability with the subject/legal representative via a telephone or a telemedicine call in order to obtain explanations regarding any discrepancies in compliance with the dosing regimen.

If a subject is found to be persistently noncompliant (defined as ≤85% or ≥115% compliant with dosing schedule), the sponsor, in conjunction with the investigator, will make a decision as to whether the subject should be withdrawn from the study.

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

If nausea or vomiting occurs during the study, antiemetic therapy with Ondansetron (Zofran®, GlaxoSmithKline, Philadelphia, PA) is allowed. Ondansetron (Zofran) is not to be used prophylactically.

Use of a topical anesthetic (eg, EMLA®, AstraZeneca, Wilmington, DE) is permitted to treat the venous puncture or indwelling venous catheter site prior to the needle stick.

If medication is medically indicated, the subject must inform the investigator immediately.

All concomitant medication and treatment must be recorded in the appropriate study documents (ie, eCRF and source document).

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Neuroleptics
- Antidepressants
- Anxiolytic drugs
- Opioids or opioid agonists
- MAO inhibitors
- Sedative antihistamines
- Benzodiazepines
- Hypnotics
- Anticonvulsants
- Central alpha-adrenergic agonists
- Melatonin
- Psychostimulant therapy, eg, for ADHD

Therapy that becomes necessary, in the investigator's opinion, during the course of the study must not be refused to a subject. The subject's participation in this study may be discontinued in such a case.

7.8.3 Rescue medication

Not applicable.

7.9 Blinding

This is a double-blind, placebo-controlled study. Subjects will be treated with either rotigotine transdermal patches or matching placebo patches.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details (ie, subject-related information about assigned kit numbers as listed in the randomization schedule) will be allocated and maintained by the IRT.

UCB personnel, as well as contract research organization (CRO) personnel involved in the study for clinical monitoring, will be blinded to the treatment assignment with the following exceptions:

- Sponsor Clinical Study Supplies Coordinator and personnel directly involved in manufacturing/packaging of the IMP
- Bioanalytical personnel involved in the bioanalytical analysis of the PK samples
- Sponsor pharmacovigilance personnel reporting SAEs to regulatory authorities
- IRT services personnel

7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IRT. The study site will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The clinical project manager (CPM) will be informed immediately via the IRT when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the investigator must be recorded in the source documents and on the Study Termination eCRF page.

An emergency envelope (or equivalent) containing the randomization code will be printed for each subject in a double-blind study and must not be broken, except for emergency situations.

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The IRT will generate individual assignments for subject kits of study drug, as appropriate, according to the visit schedule.

To enroll a subject (Visit 1), the investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject (Visit 2/Baseline), the investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the

investigator or designee of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study.

For Visit 2, there is a visit window of +3 days to allow for direct-to-subject shipment of study medication. Visit 3/Day 1 is the first day of study medication exposure.

8 STUDY PROCEDURES BY VISIT

8.1 Screening Period

Prior to any study activities, subjects will be asked to read and sign an Informed Consent form and/or Assent form that has been approved by an IRB/IEC and which complies with regulatory requirements. See Section 14.1 for a description of the informed consent process for the remote study model.

Subjects will be given adequate time to consider any information concerning the study, given to them by the investigator or designee. As part of the Informed Consent procedure, subjects will be given the opportunity to ask the investigator any questions regarding potential risks and benefits of participation in the study.

Once consented, study supplies, including screening lab kits and study instructions, will be shipped out to the subject/legal representative. The initial shipment of study supplies will include the study-issued smartphone which subjects/legal representatives will utilize throughout the study to communicate with the study team and to complete various study procedures, such as questionnaires. The telemedicine functionality of PLATFORM (see Section 2 for an overview) may also be used for the designated study visits. Subject/legal representative will return the smartphone to the study site once study participation is completed. Additional supplies will be sent to the subject/legal representative as needed throughout the study.

Subjects who have been screened but not randomized may be rescreened with the permission of the Study Physician or representative.

8.1.1 Visit 1 (Day -28 to Day -1)

The following assessments will be performed:

- Obtain informed consent. See Section 14.1 for a description of the informed consent process for the remote study model.
- Demographics
- Eligibility criteria
- General medical/procedures history
- Lifestyle: caffeine, alcohol use, and smoking
- Reproductive potential and birth control

The assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs

- Neurological examination
- 12-lead ECG

For lab collections listed below, mobile study personnel will be sent to the subject's/legal representative's home for sample collections. Samples will be prepared and sent to the central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine drug screen
- Serum pregnancy test for all female subjects
- Hormone status

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Baseline/Screening version)
- IRLS
- CGI
- mMIDI

Additional assessments and procedures are listed below.

- Recording of medication and procedures. Medications and procedures will be reviewed with the subject/legal representative by the investigator/designated study staff via a telephone or telemedicine call and noted as part of the subject's study record.
- AE assessment. All AEs will be assessed and reviewed throughout the study, starting after signing the consent documents.
- Contact IRT. During the Screening Period, the IRT will be contacted to obtain an individual study identifier that will serve as the subject's ID throughout the study.

8.2 Titration Period

The visit window for Titration Visits is ±1 day per visit relative to Visit 3 (Day 1).

8.2.1 Visit 2 (Baseline)

The following assessments will be performed via telemedicine call. The visit window for Visit 2/Baseline is +3 days.

Information and procedures listed below will be collected/completed by the investigator and/or study staff, as appropriate, via a telephone or telemedicine call with the subject/legal representative. Eligibility may only be confirmed once all the procedures noted for screening are completed, and results are obtained and reviewed.

- Eligibility criteria
- Withdrawal criteria

- Menstrual function for all female subjects

Assessments listed below will be completed by either the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version)
- IRLS (at Baseline, subjects must score ≥15 on the IRLS Rating Scale [indicating moderate-to-severe RLS])
- CGI (at Baseline, Subjects must score ≥4 points on the CGI Item 1 assessment [indicating at least moderately ill])
- RLS-6
- Subject Quality of Life Questionnaire

Additional assessments and procedures are listed below.

- Recording of medication and procedures. Medications and procedures will be reviewed with the subject/legal representative by the investigator/designated study staff via a telephone or telemedicine call and noted as part of the subject's study record.
- AE assessment. All AEs will be assessed and reviewed throughout the study.
- Contact IRT. Once eligibility is confirmed (see above), the IRT will be contacted to obtain the assigned randomization number and study medication kit numbers for the Titration Period.
- Once randomization is completed, study medication for the Titration Period will be assigned and shipped to the subject/legal representatives home for receipt on Day 1. See Section 7.5 for a description of the direct-to-subject shipment process for the remote study model.

8.2.2 Visit 3 (Day 1)

Visit 3/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 3/Day 1.

The following assessments will be performed.

- Withdrawal criteria
- C-SSRS (Since Last Visit version)

The subject will apply their first patch during the visit under the supervision of the investigator (or designee) via a telemedicine call.

8.2.3 Visit 4 (Day 8) and Visit 5 (Day 15)

Subjects will be contacted via telemedicine call. The following assessments will be performed.

- Withdrawal criteria
- C-SSRS (Since Last Visit version)
- Recording of medication and procedures

- AE assessment

8.3 Maintenance Period

The visit window for visits during the Maintenance Period is ±2 days per visit.

8.3.1 Visit 6 (Day 22)

The following assessments will be performed.

Information and procedures listed below will be collected/completed by the investigator and/or study staff, as appropriate, via a telephone or telemedicine call with the subject/legal representative.

- Withdrawal criteria
- Menstrual function for all female subjects

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Vital signs
- Body weight, height, and BMI
- Safety laboratory tests
- Urine pregnancy test for all female subjects
- PK sampling–record sampling time, time of application of study medication, and application site of study medication in eCRF

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version)
- IRLS
- CGI
- RLS-6
- mMIDI
- Subject Quality of Life Questionnaire

Additional assessments and procedures are listed below.

- Recording of medication and procedures. See Section 8.2.1.
- AE assessment. See Section 8.2.1.
- Contact IRT. The IRT will be contacted to obtain study medication kit numbers for the Maintenance Period.

- Dispense study medication. Study medication for the Maintenance Period will be distributed. See Section 7.5 for a description of the direct-to-subject shipment process for the remote study model.
- Return any unused study medication. Subjects/legal representatives will return the unused study medication patches remaining as part of the medication kits, along with the kit itself. Upon receipt of this return, designated study staff will review drug accountability with the participant via a telephone or telemedicine call to obtain explanations regarding any discrepancies in compliance with the dosing regimen.

8.3.2 Visit 7 (Day 50) and Visit 8 (Day 78)

The following assessments will be performed at Visit 7 and Visit 8 via telemedicine call.

Information and procedures listed below will be collected/completed by the investigator and/or study staff, as appropriate, via a telemedicine call with the subject/legal representative.

- Withdrawal criteria

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version)
- IRLS
- CGI
- RLS-6

Additional assessments and procedures are listed below.

- Recording of medication and procedures. See Section 8.2.1.
- AE assessment. See Section 8.2.1.
- Contact IRT. The IRT will be contacted to obtain study medication kit assignments.
- Dispense study medication. Study medication for the Maintenance Period will be distributed See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return any unused study medication. See Section 8.3.1.

8.3.3 Visit 9 (Day 106)/End of Maintenance

The following assessments will be performed.

Information and procedures listed below will be collected/completed by the investigator and/or study staff, as appropriate, via a telephone or telemedicine call with the subject/legal representative.

- Withdrawal criteria
- Menstrual function for all female subjects

Assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine pregnancy test for all female subjects
- Hormone status
- PK sampling–record sampling time, time of application of study medication, and application site of study medication in eCRF

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version)
- IRLS
- CGI
- RLS-6
- mMIDI
- Subject Quality of Life Questionnaire

Additional assessments and procedures are listed below.

- Recording of medication and procedures: See Section 8.2.1.
- AE assessment: See Section 8.2.1.
- Contact IRT: The IRT will be contacted to obtain study medication kit numbers for the Taper Period.
- Dispense study medication for the Taper Period. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return any unused study medication

8.4 Taper Period (Day 106 to Day 110)

The Taper Period, which will last up to a maximum of 4 days, will start on the day after Visit 9 and will consist of a telemedicine call. The de-escalation study medication to be taken during the Taper Period will be dispensed at Visit 9.

8.5 Safety Follow-Up Visit (if applicable)

The visit window for Safety Follow-Up Period is 30 days±5 days relative to the end of the Taper Period. Following dose de-escalation, subjects may be eligible to participate in the open-label, long-term follow-up study (RL0007) at any time prior to the Safety Follow-Up Visit (see Section 5). The Safety Follow-Up Visit is for subjects not entering RL0007.

Information listed below will be collected by the investigator and/or study staff, as appropriate, via a telephone or telemedicine call with the subject/legal representative.

- Menstrual function for all female subjects

The assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine pregnancy test for all female subjects
- Hormone status

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version)

Additional assessments and procedures are listed below.

- Recording of medication and procedures. See Section 8.2.1.
- AE assessment. See Section 8.2.1.
- Contact IRT. The IRT is contacted to process the subject's completion of the study.
- Return unused study medication. See Section 8.3.1.

8.6 Withdrawal Visit

Procedures for a withdrawal visit are the same as for Visit 9.

8.7 Unscheduled Visit

Assessments to be performed at an Unscheduled Visit are at the investigator's discretion.

Information listed below will be collected/completed by the investigator and/or study staff, as appropriate, via a telephone or telemedicine call with the subject/legal representative.

- Withdrawal criteria
- Menstrual function for female subjects

The assessments listed below will be completed by mobile study personnel at the subject/subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home for sample collections. Samples will be prepared and sent to the central laboratory for processing and analysis, and results will be provided to the study site.

- Vital signs
- Safety laboratory tests
- Urine drug screen
- Urine pregnancy test for female subjects
- Hormone status

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version) (required if the Unscheduled Visit is conducted due to safety or efficacy reasons)
- mMIDI

Additional assessments and procedures are listed below.

- Recording of medication and procedures. See Section 8.2.1.
- AE assessment. See Section 8.2.1.
- Contact IRT. The IRT is contacted to process the subject's completion of the study, if applicable.
- Dispense study medication (Taper Period de-escalation study medication will be dispensed at this visit). See Section 7.5 for a description of the direct-to-subject shipment process for the remote study model.
- Return any unused study medication. See Section 8.3.1.

9 ASSESSMENT OF EFFICACY

Refer to Table 5–1 for timings of all efficacy assessments.

9.1 International Restless Legs Rating Scale (IRLS)

The IRLS will be performed at Screening, Baseline (Visit 2), Visit 6, Visit 7, Visit 8, and Visit 9. The IRLS should also be performed in the event that a subject is prematurely withdrawn from the study (Withdrawal Visit).

The IRLS was developed by the International RLS Study Group and was validated in a large-scale study (Walters et al, 2003). The IRLS is intended to evaluate, in a standardized way, the subjective intensity of major symptoms of RLS and, in 2 items (9 and 10), the impact of the disease on subjects' functioning in daytime activities by use of a 5-point scale for each of a total of 10 items:

1. Discomfort in arms and legs due to RLS
2. Urge to move
3. Relief of symptoms by movement
4. Sleep disturbances due to RLS
5. Fatigue and somnolence during the day due to RLS
6. Global severity rating of RLS
7. Frequency of symptoms
8. Severity of symptoms (if present) during an average day (24 hours)
9. Impact of symptoms on daytime activities (family, home, social, job)
10. Impact of symptoms on mood (eg, angry, depressed, sad, anxious, irritable)

Each item is scored by the subject. Investigators or clinic personnel can assist the subject if he/she has difficulty understanding the items or locating the appropriate score. Scores for each item range from 0 (not present) to 4 (very severe). A sum score of all 10 items is calculated for analysis. The sum score ranges from 0 (no RLS symptoms present) to 40 (maximum severity in all symptoms).

The following ranges are used to determine severity categories:

- 0=none
- 1 to 10=mild
- 11 to 20=moderate
- 21 to 30=severe
- 31 to 40=very severe

A minimum score of 15 points (moderate) is typically required for inclusion in a study at Baseline.

Subjects should answer each item in reference to the 7 days prior to their visit. If the timeframe since the last visit is <7 days (eg, in the event of premature discontinuation), the subject should answer each item in reference to the days since their last visit.

Subjects will be classified into the following categories:

- IRLS responder: A relative reduction in IRLS total score in percentage points at the end of maintenance compared to Baseline. This categorization will be carried out for a reduction of at least 50% (that is a percentage relative change for less than or equal to -50%),
- IRLS remitter: Two types of IRLS remitter are defined: 1) an IRLS total score of 10 or less (remitter criterion 1) and 2) an IRLS total score of 0 (remitter criterion 2).

9.2 Clinical Global Impressions

The CGI Item 1 will be performed at Screening, Baseline (Visit 2), and Visit 6 through Visit 9 (Guy and Bonato, 1970).

Item 1 (Severity of Illness): Scores range from 0 to 7 as follows: 0=not assessed, 1=normal, not ill at all, 2=borderline ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill, 7=among the most extremely ill.

The CGI Item 1 is to be completed during an interview between the subject and the investigator or designee.

Note that at Baseline a minimum CGI Item 1 score of 4 points (indicating at least moderately ill) is typically required for inclusion in RLS studies.

Subjects will be classified into the following category:

- CGI Item 1 responder: A relative reduction in CGI Item 1 (severity of illness) in percentage points of at least 50% at the respective visit compared to Baseline (ie, a percentage relative change for less than or equal to –50%)

CGI is validated in mental diseases only; but it is widely used.

9.3 RLS-6

The RLS-6 will be performed at Baseline (Visit 2) and at Visit 6 through Visit 9. The RLS-6 should also be performed in the event that a subject is prematurely withdrawn from the study (Withdrawal Visit).

The RLS-6 Rating Scales is designed to assess the severity of RLS (Kohnen et al, 2003) and consists of 6 subscales. The subscales assess severity of symptoms at the following times of the day/evening: falling asleep, during the night, during the day at rest, and during the day when engaged in daytime activities. In addition, the subscales assess satisfaction with sleep and severity of daytime tiredness/sleepiness.

Scores for each of the 6 subscales range from 0 (completely satisfied) to 10 (completely dissatisfied).

Each subscale item should be scored by the subject. Investigators or clinic personnel can assist the subject if he/she has difficulty understanding the subscale. Subjects should answer each subscale in reference to the 7 days prior to their visit. If the timeframe since the last visit is <7 days (eg, in the event of premature discontinuation), the subject should answer each subscale in reference to the days since their last visit.

The change from baseline will be derived for each of the 6 subscales.

No sum score will be calculated.

Post-baseline missing values will not be imputed.

9.4 Subject Quality of Life Questionnaire

The RLS-QoL will be performed at Visit 2, Visit 6, and Visit 9. The RLS-QoL should also be performed in the event that a subject is prematurely withdrawn from the study (Withdrawal Visit).

The RLS-QoL (Kohnen et al, 2002) will be used to evaluate quality of life at these visits. This disease-specific instrument consists of 12 items. The most relevant item is a global rating of quality of life "all in all".

Further items are related to consequences of the RLS symptoms on sleep, activities of daily living, mood, and social interactions, to the consequences of disturbed sleep on everyday life and to those of tiredness during the day on mood; furthermore, consequences of pain and side effects of treatments on daily activities are to be evaluated. A final section of the questionnaire asks for evaluation of coping behavior (effort of measures to get relief from the symptoms, avoidance of social situations, changes in life style). The main outcome parameter is a total score which is calculated from all items.

10 ASSESSMENT OF PHARMACOKINETIC VARIABLES

10.1 Blood sampling for the determination of rotigotine plasma concentrations

For the determination of unconjugated rotigotine, 5.5mL of blood will be drawn prior to patch removal by venous puncture or indwelling venous catheter into lithium heparinized tubes at Visit 6 and Visit 9 (refer to Table 5–1 for timing of PK assessments). The sampling time should be recorded on the eCRF when PK samples are to be taken. The application site and time of last application of the study medication prior to the PK assessment will also be collected.

Treatment of the venous puncture or indwelling venous catheter site with a topical anesthetic (eg, EMLA) prior to the needle stick is permissible.

Details can be found in the study lab manual.

10.2 Shipment procedures

Details can be found in the study lab manual.

10.3 Bioanalytical method

Plasma concentrations of requested analytes will be determined with validated bioanalytical methods. After the sample preparation step, the target compounds are separated by a reversed-phase liquid chromatography and detected by electrospray ionization tandem mass spectrometry using multiple reaction monitoring in positive-ion mode.

11 ASSESSMENT OF SAFETY

Refer to Table 5–1 for timings of all safety assessments. In addition to the AE assessments completed at the designated study visits (see Table 5–1 and Section 8), the subjects/legal representatives are also able to contact study staff at any time via the study-issued smartphone to discuss their condition, ask questions, and/or report AEs/SAEs. All AEs and SAEs will be evaluated and reported as noted below. Based on the investigator's evaluation of the AE/SAE,

appropriate medical intervention/support measures will be instituted as necessary (ie, urgent care services, etc) and documented as part of the subject's study record.

11.1 Adverse events

11.1.1 Definitions

11.1.1.1 Adverse event

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

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the investigator from the subject's history or the Baseline Period.

11.1.1.2 Serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

(A patient admitted to a hospital, even if he/she is released on the same day, meets the criterion for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, ecg].

Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that, if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

11.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 11.1.2.3.

Table 11–1: Anticipated serious adverse events for the RLS population

MedDRA system organ class	MedDRA preferred term
Gastrointestinal disorders	Diarrhoea
Infections and infestations	Upper respiratory tract infection Bronchitis Urinary tract infection
Psychiatric disorders	Depression

MedDRA=Medical Dictionary for Regulatory Activities; RLS=Restless Legs Syndrome

11.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

11.1.2 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

11.1.2.1 Description of adverse events

When recording an AE, the investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

11.1.2.2 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

11.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol). The investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global safety database.

An Investigator SAE Report form will be provided to the investigator. The Investigator SAE Report form must be completed in English.

It is important for the investigator, when completing the SAE Report form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report form.

The investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the investigator of any SAE within this period. Serious AEs that the investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

11.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 11.6.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the investigator no longer deems that it is clinically significant, or until the subject is lost to follow up. If no follow up is provided, the investigator must provide a justification. The follow up will usually be continued for 30 days days after the subject has discontinued his/her IMP.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

11.2 Pregnancy

If an investigator is notified that a subject has become pregnant after the first intake of any IMP, the investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome form (for contact details see Serious Adverse Event reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- An early discontinuation visit should be conducted.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the early discontinuation visit.
- A Safety Follow-Up Visit should be scheduled 30 days ±5 days after the subject has discontinued her IMP.

The investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome form provided to the investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome form in which the investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain

circumstances, UCB may request that follow up is continued for a period longer than 30 days. If the subject is lost to follow up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the investigator and filed at the site. UCB's PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the investigator site file (ISF). In case of questions about the consent process, the investigator may contact the UCB/CRO contract monitor for the study. The investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see Serious Adverse Event reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

11.3 Suspected transmission of an infectious agent

With respect to the rotigotine transdermal patch, it is not likely that transmission of an infectious agent will occur in clinical practice. For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the eCRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

11.4 Overdose of investigational medicinal product

With respect to the rotigotine transdermal patch, it is not likely that significant overdosing will occur in clinical practice unless subjects forget to remove the previous day's patch; subjects should be warned against this possibility.

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

11.5 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

11.6 Laboratory measurements

A central laboratory will perform routine hematology, clinical chemistry, and hormone analyses.

It is recommended that subjects be scheduled for morning appointments to complete these procedures. However, if morning appointments are not feasible, then subjects should continue to be scheduled at approximately the same time of day as all other visits.

Treatment of the venous puncture or indwelling venous catheter site with a topical anesthetic (eg, EMLA) prior to the needle stick is permissible.

Urinalyses are performed locally using urine dipsticks. If the dipstick results are abnormal and of clinical concern, a repeat sample will be sent to the central laboratory for evaluation.

The laboratory parameters listed in Table 11–2 will be measured.

Table 11–2: Laboratory measurements

Hematology	Endocrine	Urinalysis
Red blood cell count	Estradiol[a]	Color
Hematocrit	FSH	Appearance
Hemoglobin	IGF-1	Glucose
Platelet count	LH	Protein
White blood cell count[b]	Progesterone[a]	Blood
RBC indices MCH MCV MCHC RDW	Prolactin	Ketones
	Testosterone[c]	Pregnancy test[a]
	T3	
	T4	
	TSH	
Chemistry		
ALT	Glucose	
AST	Phosphorus	
Albumin	LDH	
Alkaline phosphatase	Potassium	
Bicarbonate	Serum iron	
BUN	Sodium	
Calcium	Total cholesterol	
Chloride	Total bilirubin	
Creatinine	Total protein	
Ferritin	Transferrin	
GGT	Uric acid	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; IGF-1=insulin-like growth factor-1; LDH=lactate dehydrogenase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; MCV=mean cell volume; RBC=red blood cell; RDW=red cell distribution width; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone

[a] Females only. Serum pregnancy test at Screening and urine pregnancy test at all other visits. A positive urine pregnancy test must be confirmed by a serum pregnancy test.

[b] With differential.

[c] Males only.

11.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 11.1.1.3), and, if applicable, also reported as an SAE (see Section 11.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.6.1.4).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable eCRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

The table below summarizes the approach to investigate PDILI.

Table 11–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.6.1.3.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥8xULN	NA	NA				
≥3xULN	NA	Yes		Immediate, temporary or permanent, IMP discontinuation.		
≥3xULN (and ≥2x baseline) and <5xULN	<2xULN	No	Discussion with Medical Monitor required if the criterion that allows for IMP continuation is met.	Further investigation – immediate IMP discontinuation not required (see Section 11.6.1.2).	Not required unless otherwise medically indicated (at discretion of investigator).	
≥5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required.	Immediate, permanent IMP discontinuation.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours (see Section 11.6.1.3).	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]

Table 11–3: Required investigations and follow up for PDILI

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug-induced liver injury; ULN=upper limit of normal

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 11.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the investigator and UCB responsible physician. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.6.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.6.1.3) and SAE report (if applicable).

11.6.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11–3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

11.6.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 11–4 (laboratory measurements) and Table 11–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed:

Table 11–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)

Table 11–4: PDILI laboratory measurements

	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 11–5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)

Table 11–5: PDILI information to be collected

New or updated information
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

11.6.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 11–3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.7 Other safety measurements

11.7.1 12-lead electrocardiogram values

If a subject develops a clinically relevant ECG abnormality that is confirmed by a repeat ECG performed at least 1 hour later, the subject should be excluded from the study. Bazett's formula must be used for correction of QT intervals.

The ECGs will be centrally read. The investigator will confirm the computerized measurements of PR, QRS, QT, and QT interval corrected for heart rate using Bazett's formula (QTcB) intervals (assessed as the mean of 3 to 5 beats).

11.7.2 Vital signs

Vital sign assessments include supine and standing BP measurements and pulse rate. At each visit, vital signs will be assessed. The assessment should be taken as follows: The subject should initially rest for 2 minutes. While the subject is supine, the BP and pulse rate should be measured after 1 minute and then again after 5 minutes (ie, 4 minutes between the 2 measurements). The subject should then be asked to stand and the BP and pulse rate should be taken 1 minute and 3 minutes post standing (ie, 2 minutes between measurements).

Assessment of orthostatic reaction will be performed at all visits as follows: After the 5-minute measurement in supine position, the subject is asked to stand up; BP and pulse rate are measured 1 and 3 minutes after standing. The 5-minute BP supine values will be compared with the values after standing. A drop in systolic BP of ≥20mmHg and/or a drop of ≥10mmHg in diastolic BP after 1 and/or 3 minutes in standing position is indicative of orthostatic hypotension.

Subjects who develop clinically relevant symptomatic hypotension during the course of the study should be withdrawn (see Section 6.3).

11.7.3 Physical and neurological examinations

A brief physical examination of all body systems will be performed.

The neurological examination may include assessment of mental status, cranial nerves, plantar reflexes, deep tendon reflexes, muscle strength, gait, coordination/balance, involuntary movements, and sensory perception.

11.7.4 Hormone status

It is recommended that subjects be scheduled for morning appointments to assess hormone status (beta-17-estradiol [females only], progesterone [females only], follicle-stimulating hormone [FSH], luteinizing hormone [LH], prolactin, triiodothyronin [T3], thyroxine [T4], thyroid-stimulating hormone [TSH], testosterone [males only], and insulin-like growth factor-1 [IGF-1]). However, if morning appointments are not feasible, then subjects should continue to be scheduled at approximately the same time of day as all other visits.

11.7.5 Modified Minnesota Impulsive Disorders Interview

The mMIDI has been previously used in Parkinson's subjects to monitor for development of ICDs (Christenson et al, 1994). The mMIDI is applicable for both initial identification of a potential ICD and for monitoring ICDs during a clinical study. This mMIDI focuses on the 5 most common ICDs which may be associated with dopamine agonist use: compulsive buying, compulsive gambling, compulsive eating, hypersexuality, and punding (nonsense repetitive behavior). The mMIDI will be used only to identify potential impulsive control AEs. The mMIDI will be completed according to the schedule of study procedures (Table 5–1).

For each of the 5 modules, a gateway question is asked (eg, Do you gamble?). If a gateway question is answered "no", that module ends. Any positive answer after a gateway question would affirm the ICD and the subject would move to the next step, which is formal diagnosis (referral for a structured clinical interview such as the Structured Clinical Interview for DSM-IV Axis II Personality Disorders or other applicable structured clinical interview for the diagnosis of ICDs). The instrument should be administered by a physician or a clinical psychologist trained to administer the instrument.

If the subject has a positive mMIDI and a positive structured clinical interview or if the subject refuses the structured clinical interview, it would be up to the investigator to determine if the subject should be withdrawn from the study. Positive findings from the structured interview must be recorded as AEs, and monitored for degree of changes during the study.

If the subject was referred for a structured clinical interview previously during the study, the investigator may use his/her discretion regarding the need to refer the subject for a further structured interview.

11.7.6 Menstrual function

Questions regarding changes in menstrual function in females will be asked.

11.7.7 Assessment of suicidal ideation and behavior

Suicidal ideation and behavior will be assessed by trained study personnel using the C-SSRS. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The C-SSRS will be completed according to the tabular schedule of study assessments (see Table 5–1).

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 Adherence to protocol

The investigator should not deviate from the protocol. However, the investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

12.2 Monitoring

Monitoring of the study will be delegated by UCB to a CRO. The CRO will monitor the study to meet the CRO's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

The investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities' regulations, and investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

For the remote study model, a remote monitoring option is available. All study materials, including the ISF, drug accountability records, electronic source documentation, etc will be available for remote monitoring with view-only access, with training provided prior to access being granted, Study staff will be available to meet via telephone call or telemedicine call.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording and should not be obscured. Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents, whether paper or electronic, are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, drug accountability records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Source documents that are computer generated and stored electronically must be available for review by the monitor (eg, ECG reports). The technology platform used in this study (PLATFORM, see Section 2 for an overview) has multiple levels of functionality, including electronic source documentation. All information and data collected in PLATFORM is kept securely, with the required privacy measures in place per regulations.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

12.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject records, recordings from automated instruments, tracings [ECG], x-ray films, laboratory reports). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 Case Report form completion

The investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRFs and in all required reports.

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the investigator's review and approval (by means of a password/electronic signature) will be reapproved by the investigator.

The investigator should maintain a list of personnel authorized to enter data into the eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

12.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

12.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded as part of the Subject Screening and Enrollment log.

The investigator will keep a Subject Identification Code list. This list remains with the investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded as part of the subject's study record. These data should identify the study and document the dates of the subject's participation.

12.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

12.5 Archiving and data retention

The investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the investigator 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 IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's study master file.

12.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH-GCP, and applicable regulatory requirements.

The investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the investigator will immediately inform UCB (or designee).

12.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

13 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

13.1 Definition of analysis sets

The following analysis sets will be defined:

- Enrolled Set (ES): all subjects with a signed informed consent form and demographic data.
- Randomized Set (RS): all subjects from the ES who have been randomized.
- Safety Set (SS): all subjects from the RS who have at least 1 patch (rotigotine or placebo) applied. This population will be used for all safety analyses.

Full Analysis Set (FAS): all subjects from the SS who have a valid IRLS score and a valid CGI Item 1 score at Baseline and a valid post-Baseline IRLS score and a valid post-Baseline CGI Item 1 score. This population is the primary population for efficacy analysis.

- Per Protocol Set (PPS): all subjects from the FAS with no important protocol deviations (as specified in the data evaluation meeting) that could affect the co-primary variables and hence the efficacy evaluation. This population is the secondary population for efficacy analysis.

13.2 General statistical considerations

Datasets will be analyzed using SAS version 9.4 or higher.

A complete set of raw data listings containing both, all documented data and all calculated data (eg, difference from Baseline) will be generated. In general, summary statistics (n [number of available measurements], arithmetic mean, standard deviation [SD], median, minimum, and maximum) for quantitative variable and frequency tables for qualitative data will be presented by treatment.

13.3 Planned efficacy analyses

13.3.1 Analysis of the co-primary efficacy variables

Mean changes from Baseline to the end of the Maintenance Period in IRLS sum score and CGI (Item 1) in the 2 rotigotine arms (2mg/24h and 3mg/24h) will be compared with placebo to demonstrate superior efficacy of rotigotine.

The primary analysis of each co-primary variable will be based on a mixed model repeated measures (MMRM) analysis of covariance (ANCOVA) that includes terms for treatment group, visit, the respective Baseline score, and the interaction between treatment group and visit. The model will define patient as a random effect and utilize an unstructured covariance pattern. From this MMRM ANCOVA, treatment least-square (LS) means (with 95% confidence intervals [CI]) will be calculated and 1-sided 2 sample t-test will be performed (significance level 0.025) to test

the superiority of the rotigotine dose levels versus placebo, starting with 3mg/24h. The corresponding p-values will also be calculated.

The null hypotheses at each dose level are (H0): rotigotine is not superior compared to placebo. The alternative hypotheses are (H1): rotigotine is superior to placebo. Both co-primary endpoints must demonstrate significant results (at significance level 0.025) to demonstrate superiority of this dose level of rotigotine over placebo.

If the 3mg/24h dose is successful, the 2mg/24h dose level will be tested in the same way. Since both hypotheses have to be rejected in order to continue, multiplicity adjustment is not needed for the 2 hypotheses at each dose level. The multiplicity based on the two dose levels will be covered by applying the hierarchical approach (closed test procedure).

For subjects who prematurely withdraw for any reason before end of Maintenance, data collected during the Withdrawal Visit will be used to impute measurements at the next consecutive visit.

IRLS or CGI-1 measurements must be performed no longer than 1 day after the last patch removal to be utilized for analysis (valid measurements).

The above analyses will be performed on the FAS and the PPS. The primary analysis will be considered the analysis on the FAS.

13.3.2 Analysis of the secondary efficacy variable

For the secondary variables change from Baseline to end of the Maintenance Period in CGI Item 1 and RLS-6 an ANCOVA will be performed as described for the analysis of the primary variable, however PPS analyses will not be performed.

13.3.3 Other efficacy variables

The other efficacy variables listed will be analyzed in a descriptive manner. Summary statistics will be provided, statistical tests comparing rotigotine arms with placebo will be performed and the corresponding p-values will be provided for descriptive purposes only.

- Change from Baseline in CGI Item 1 by visit*
- Change from Baseline in RLS-6 Rating Scales by visit*
- Change from Baseline in IRLS sum score by visit*
- IRLS Responder by visit
- IRLS Remitter by visit and by definition (see previous)
- CGI scale Item 1 Responder
- *For the IRLS, CGI, and RLS-6 the EoM Visit is already covered under primary and secondary variables.

13.4 Planned safety and other analyses

All analyses for safety and other non-efficacy variables will be performed using the subjects in the SS.

13.4.1 Safety analyses

Adverse events will be reported in frequency tables as the number and percentage of subjects reporting TEAEs by treatment group. Additionally, frequency tables for serious TEAEs, non-serious TEAEs, TEAEs leading to discontinuation of study medication, TEAEs by intensity and TEAEs by relationship to treatment will be provided by treatment group.

Descriptive statistics on change from Baseline in laboratory data, including hormone status, will be summarized by visit and treatment group. Post-Baseline clinical significant abnormalities will be presented by treatment group.

Vital signs variables and their change from Baseline will be presented using descriptive statistics by visit and treatment group. The number and percentage of subjects meeting orthostatic hypotension criteria will also be presented.

ECG and its change from Baseline will be presented using descriptive statistics by visit and treatment group. The number and percentage of subjects with post-Baseline clinical significant abnormalities will be presented by treatment group.

Body weight, height, and BMI and their change from Baseline will be presented using descriptive statistics by visit and treatment group. Clinically significant values will be reported.

13.4.2 Other analyses

Prior and concomitant medication as well as medical history will be summarized using frequency tables. Demographic and baseline characteristics will be summarized using descriptive statistics.

Plasma concentration of unconjugated rotigotine will summarized by dose levels and visit. In addition, these concentrations may be used for population PK-PD analyses.

Summary statistics for Subject Quality of Life Questionnaire will be provided.

13.5 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK/PD outcomes (if applicable) for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation. All important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

13.6 Handling of dropouts or missing data

Rules for imputation of missing data will be detailed in the SAP.

No imputation will be implemented for missing values in other efficacy variables or safety variables. However, rules for date imputations to allow the derivation of variables (eg, age and TEAEs) will be implemented.

Dropouts will not be replaced during the course of the study.

13.7 Planned interim analysis and data monitoring

An interim analysis for futility will be performed with approximately 33% of the planned number of evaluable subjects; recruitment will not be stopped for the interim analysis. The interim analysis will have three possible outcomes:

- Stop the study early for futility because rotigotine treatment at 3mg/24h meets the futility criteria (ie, no demonstrated benefit between active treatment and placebo to be expected at final analysis) regarding the primary objective of the study
- Stop recruitment into the rotigotine 2mg/24h arm for futility because rotigotine treatment at 2mg/24h seems futile regarding the primary objective of the study,
- Continue the study as planned.

No further changes to the protocol (eg, sample size adjustment) will be made as a result of the interim analysis.

The interim analysis will be conducted as soon as the end of the Maintenance/Premature Withdrawal Visit has been documented for 45 evaluable patients. The interim analysis will be performed on the data for the primary efficacy variable IRLS only and CGI Item 1 will not be considered. In case futility is achieved for the IRLS, this would also hold true for the CGI, since a lower effect size index for CGI is anticipated.

In the interim analysis, the change from Baseline to the end of the Maintenance Period in the score of the IRLS will be investigated. Estimates of treatment effect will be obtained separately for the two active treatment arms and Placebo from an MMRM ANCOVA model as described in Section 13.3.1. Furthermore, the conditional power under the anticipated effect (anticipated effect and standard deviation will be utilized) according to Lan and Wittes (Siu and Lan, 2001) will be calculated for each of the treatment arms. The conditional power under the anticipated effect refers to the probability of concluding a positive result on the IRLS at the end of the study, assuming that the assumptions for the sample size estimation holds true.

The continuation criterion for each treatment arm is defined as applying both of the following conditions regarding the change from Baseline to the end of the Maintenance Period in the score of the IRLS:

- Treatment difference between the respective active group and placebo ≥2.0 points
- Conditional power under anticipated effect ≥60 %

If at least 1 of these conditions fails, the continuation criterion is not met. Table 13–1 shows the possible outcomes of the interim results and the corresponding decision rules.

Table 13–1: Decision rules at the interim analysis

Interim result	Decision
Failed continuation criterion for the 3mg/24h arm	Stop the study early
Met continuation criterion for the 3mg/24h arm Failed continuation criterion for the 2mg/24h arm	Remove the 2mg/24h arm and continue the study with the 3mg/24h arm and the placebo arm

Table 13–1: Decision rules at the interim analysis

Interim result	Decision
Met continuation criterion for the 3mg/24h arm Met continuation criterion for the 2mg/24harm	Continue the study as planned (with 3mg/24h and 2mg/24h arms plus placebo)

The interim analysis will be performed by an independent unblinded statistician not involved in any other study activity. Access to the interim results will be restricted to the statistician performing the analysis.

The study team will remain blinded and will be informed of the decision (stop the study early, stop a dose arm or continue the study as planned) without any supporting information. Details of the analysis will only be disclosed to the sponsor after study unblinding and will be provided in the clinical study report.

13.8 Determination of sample size

The sample size estimate is based on the efficacy results observed in the adult RLS Phase 3 confirmatory study SP792, which was conducted in the USA. In this study, a range of rotigotine doses were compared to placebo.

The sample size calculation assumes that adolescent and adult patients will show a similar effect of rotigotine with respect to IRLS score and CGI (item 1) changes from Baseline in comparison to placebo, with a similar proportion of patients not included in the primary analysis.

In the adult study, the observed difference between the 3mg/24h rotigotine group and placebo in the change from Baseline to end of the 3-month Maintenance Period in IRLS sum score was 5.9. Already a difference between rotigotine and placebo of 4.0 points can be considered as clinically relevant. The common Standard Deviation (SD) estimate in the adult study was 7.9. For the CGI (Item 1), the difference between 3mg/24h rotigotine group and placebo was 0.6 with a SD of 1.2.

With these assumptions, a sample size of 45 evaluable patients in each group will provide a power of 93% for the IRLS endpoint, and a power of 87% for the CGI (Item 1) endpoint in the 3mg/24h dose. Assuming independence of the 2 endpoints will result in a power of 80% for the analysis of the co-primary variables. Since it is known that the 2 endpoints will have a relatively high correlation (approximately 0.7), the calculated 80% is a conservative estimator for the power.

Assuming similar effects for the 2mg/24h dose group, the conditional power for the 2mg/24h dose group is also 80% with an overall power for the study >60%. To obtain 135 evaluable subjects (ie, FAS), 138 patients have to be randomized (assuming approximately 2% of the randomized subjects cannot be utilized).

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the investigator.

For those subjects who are assessed as preliminarily eligible per the IRB-approved prescreening script, contact information will be collected, including a valid email address of the subject/legal representative (eg, parent or guardian). A secure link to the eConsent web portal will be sent via email, along with unique login credentials. The subject/legal representative will receive a prompt to change the temporary assigned password upon first login. The informed consent materials will be presented in the eConsent portal through an electronic rendition of the IRB-approved consent documents. The study investigator and/or designated staff will complete the informed consent process with the subject/legal representative by telephone. Subjects who agree to take part in the study will provide their handwritten signature using a computer mouse, touchscreen, or stylus on a computer or tablet in the designated signature block; the legal representative will complete the handwritten signature in the same manner; and the consenter will countersign. If a legal representative agrees for the adolescent to take part in the study, but the adolescent does not wish to participate, then he or she cannot be enrolled.

The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

14.2 Subject identification cards

Upon signing the Informed Consent and Assent form (as applicable), the subject or legal representative will be provided with a subject identification card in the language of the subject. The investigator will fill in the subject identifying information and medical emergency contact information. The investigator will instruct the subject to keep the card with him/her at all times.

14.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator/UCB will forward copies of the protocol, Informed Consent form, Investigator's Brochure, investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the investigator or the sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

14.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

14.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

15 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the investigator and/or CRO agreements, as applicable.

16 REFERENCES

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17 APPENDICES

17.1 Protocol Amendment 1

Rationale for the amendment

The main purpose of this substantial amendment was to change the ferritin level at Visit 1/Screening from <50ng/mL to below the lower limit of normal.

Other changes included in this amendment are as follows:

- Sponsor contact information has been updated.
- Added headings for primary and other safety variables. Clarified that AEs are treatment emergent. Categorized occurrence of TEAEs and TEAEs leading to withdrawal as primary safety variables. The remaining safety variables were categorized as other.
- Changed the eC-SSRS to the C-SSRS.
- Addition of urine drug screen at Unscheduled Visits.
- Clarified that the smartphone technology will be used in combination with visits from mobile study personnel to subjects'/legal representatives' homes. Visits to local health care providers or Patient Service Centers will not be conducted during this study.
- Clarified that a serum pregnancy test is to be performed in females at Screening and urine pregnancy test at all other visits. A positive urine pregnancy test must be confirmed by a serum pregnancy test.
- Added a description of the Where's My Patch (WMP) app.
- Removed BMI of <95th percentile for his or her age group, according to the Child and Teen BMI calculator as Inclusion Criterion #5.
- Clarified that the washout period for supplemental iron is 1 month prior to Baseline in Exclusion Criterion #10a.
- Added secondary RLS (eg, due to renal insufficiency [uremia], iron deficiency, or rheumatoid arthritis as Exclusion Criterion #13.
- Added a lifetime history of suicide attempts or suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the C-SSRS at Screening as Exclusion Criterion #14.
- Added taking a prohibited concomitant medication and the washout period as Exclusion Criterion #15.
- Clarified that subjects who have been screened but not randomized may be rescreened with the permission of the Study Physician or representative.
- Added RBC indices (mean corpuscular hemoglobin; mean corpuscular hemoglobin concentration; mean cell volume; cell distribution width) to the laboratory measurements.
- Typographic errors and changes of an editorial nature were made.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- Changed the eC-SSRS to the C-SSRS.

Specific changes

Change #1

Page 2, STUDY CONTACT INFORMATION:

Sponsor Study Physician

Name:	[redacted], [redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Strasse 10, 40789 Monheim, Germany
Phone:	[redacted]
Email:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Strasse 10, 40789 Monheim, Germany
Phone:	[redacted]
Email:	[redacted]

Change #2

Page 2, STUDY CONTACT INFORMATION:

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Strasse 10, 40789 Monheim, Germany
Phone:	[redacted]
Email:	[redacted]

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB Celltech 216 Bath Road, Slough SL1 3WE, UK
Phone:	[redacted]
Email:	[redacted]

Change #3

Section 2, INTRODUCTION

Last paragraph, last sentence

This technology will be used in combination with visits from mobile study personnel to subjects'/legal representatives' homes, subjects'/legal representatives' visits to their local healthcare provider, and/or subjects'/legal representatives' visits to national Patient Service Centers for various lab collections and designated study procedures. Patient Service Center locations are available across the country and provide standardized collection and processing of various laboratory samples and other standard procedures, such as collection of vital signs, etc.

Has been changed to:

This technology will be used in combination with visits from mobile study personnel to subjects'/legal representatives' homes.

Change #4

Section 4.2, Safety variables

Safety variables include:

- AEs
- Withdrawals due to AEs
- Changes from Baseline in 12-lead ECGs
- Changes from Baseline in vital signs (including assessment of orthostasis)
- Changes from Baseline in laboratory data (hematology, blood chemistry, and urinalysis)
- Changes from Baseline in hormone status
- Changes from Screening in body weight, height, and BMI
- Changes from Baseline in mMIDI
- Changes in menstrual function for all female subjects

Has been changed to:

4.2.1 Primary safety variables

- Occurrence of TEAEs
- TEAEs leading to withdrawals

4.2.2 Other safety variables

- Changes from Baseline in 12-lead ECGs
- Changes from Baseline in vital signs (including assessment of orthostasis)
- Changes from Baseline in laboratory data (hematology, blood chemistry, and urinalysis)
- Changes from Baseline in hormone status
- Changes from Screening in body weight, height, and BMI
- Changes from Baseline in mMIDI
- Changes in menstrual function for all female subjects

Change #5

Section 5.1, Study description

Second, third, and fourth paragraphs

The study will be conducted using the remote study model, which uses telemedicine technology (ie, NORA, see Section 2 for an overview) for interactions between the investigator/study staff and study subjects/legal representatives. Additionally, subjects/legal representatives will visit local healthcare facilities, such as local healthcare provider's offices/clinics and local Patient Service Centers, to complete designated study procedures (eg, neurological exams, physical exams, and ECGs with local healthcare providers; lab collections and vital signs at Patient Service Centers). As an alternative option to Patient Service Centers, mobile study personnel may visit subjects'/legal representatives' homes to complete certain study procedures.

The study will begin with a Screening Period of at least 7 days (maximum of 28 days) prior to Visit 2/Baseline to ensure homogeneous baseline conditions can be established for all subjects. Subjects with prior intake of any dopamine agonists must discontinue therapy at least 14 days prior to Visit 2/Baseline. Subjects taking L-dopa must discontinue therapy at least 7 days prior to Visit 2/Baseline.

The Screening Period will be followed by the Titration Period. Subjects will receive their first dose of study medication following Baseline at Visit 3/Day 1. Subjects will be initiated either on placebo or 1mg/24h rotigotine. The dose of rotigotine taken by subjects randomized to rotigotine will then be up-titrated on a weekly basis by 1mg/24h at a time to 2mg/24h or 3mg/24h, depending on the subject's assigned dose level.

Has been changed to:

The study will be conducted using the remote study model, which uses telemedicine technology (ie, NORA, see Section 2 for an overview) for interactions between the investigator/study staff and study subjects/legal representatives. Mobile study personnel may visit subjects'/legal

representatives' homes to complete certain study procedures (eg, neurological exams, physical exams, ECGs, lab collections, and vital signs).

The study will also utilize a reminder app to help maximize retention of study subjects and limit dropouts. The app, located on the study smartphone, called Where's My Patch (WMP) will help encourage subject adherence to study medication administration by reminding them to place patches at their prespecified time each day. It also provides a body map to record daily patch locations as a visual reminder of where patches have already been placed over the past 14 days and to facilitate patch site rotation. Patch location data will only be retained locally on the smartphone and then automatically deleted after 14 days. Subject use of the MWP app will be encouraged, but not required.

The study will begin with a Screening Period of at least 7 days (maximum of 28 days) prior to Visit 2/Baseline to ensure homogeneous baseline conditions can be established for all subjects. Subjects with prior intake of any dopamine agonists must discontinue the therapy at least 14 days prior to Visit 2/Baseline. Subjects taking L-dopa must discontinue the therapy at least 7 days prior to Visit 2/Baseline. Discontinuation of therapy must be driven by the subject's medical needs and not undertaken with the purpose of making a potential subject eligible for this study.

The Screening Period will be followed by the Titration Period. Subjects will receive their first dose of study medication at Visit 3/Day 1. Subjects will be initiated either on placebo or 1mg/24h rotigotine. The dose of rotigotine taken by subjects randomized to rotigotine will then be up-titrated on a weekly basis by 1mg/24h at a time to 2mg/24h or 3mg/24h, depending on the subject's assigned dose level.

Change #6

Section 5.2, Schedule of assessments

Table 5–1: Schedule of Assessments

Assessment	Screening Period	Rand	Titration Period[a]			Maintenance Period[a]			Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls					Telemedicine Calls			Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
	Day -28 to Day -1	Day 0	Day 1	Day 8	Day 15	Day 22	Day 50	Day 78	Day 106	Day 110		
…												
Urine drug screen	X											
Urine Pregnancy Test[d] (hCG)	X					X			X		X	X
…												
Contact IRT	X	X				X			X		X	X
Dispense study medication			X[g]			X[g]			X[g]			
Return unused study medication						X	X	X	X		X	X

Table 5–1: Schedule of Assessments

Assessment	Screening Period	Rand	Titration Period[a]			Maintenance Period[a]			Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls					Telemedicine Calls			Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
	Day -28 to Day -1	Day 0	Day 1	Day 8	Day 15	Day 22	Day 50	Day 78	Day 106	Day 110		

BL=Baseline; BMI=body mass index; CGI=Clinical Global Impressions; ECG=electrocardiogram; eCRF=electronic Case Report form; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; hCG=human chorionic gonadotropin; IRLS=International Restless Legs Scale; IRT=interactive response technology; mMIDI=Modified Minnesota Impulsive Disorder Interview; PK=pharmacokinetic; Rand=randomization; RLS=Restless Legs Syndrome; V=Visit; WD=withdrawal

Note: For Visit 2, there is a visit window of +3 days to allow for direct-to-subject shipment of study medication. Visit 3/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 3/Day 1.

Note: Visit 5 is the end of the Titration Period and start of the Maintenance Period. Visit 8 is the end of the Maintenance Period and start of the Taper Period.

Note: All visits are via telemedicine calls, with the exception of Visit 1, Visit 6, Visit 9, SFU, and unscheduled visits.

[a] The visit window for Titration Visits is ±1 day per visit relative to Visit 3 (day of first dose). The visit window for visits during the Maintenance Period, including the End of Maintenance Visit, is ±2 days per visit. The Taper Period, which will last up to a maximum of 4 days, will start on the day after the End of Maintenance Visit. Note that there are no planned visits during the Taper Period. The visit window for Safety Follow-Up Period is 30 days±5 days relative to the end of the Taper Period. Following dose de-escalation, subjects may be eligible to participate in the open-label, long-term follow-up study (RL0007) at any time prior to the Safety Follow-Up Visit (see Section 5). The Safety Follow-Up Visit is for subjects not entering RL0007.

[b] Assessments to be performed are at the investigator's discretion.

[c] eC-SSRS is required if the Unscheduled Visit is conducted due to safety or efficacy reasons.

[d] Urine pregnancy test and menstrual function for all female subjects.

[e] At the time of PK sampling, sampling time, time of application of study medication, and application site of study medication should be recorded in the eCRF.

[f] At Baseline, subjects must score ≥15 on the IRLS Rating Scale (indicating moderate-to-severe RLS) and must score ≥4 points on the CGI Item 1.

[g] Study medication to be shipped to subject's home to be available no later than this date.

Has been changed to:

Table 5–1: Schedule of Assessments

Assessment	Screening Period (+1 day)	Rand (+3 days)	Titration Period[a] (±1 day)		EOT/ SOM	Maintenance Period[a] (±2 days)			Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls					Telemedicine Calls			Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
	Day -28 to Day -1	Day 0	Day 1	Day 8	Day 15	Day 22	Day 50	Day 78	Day 106	Day 110		
…												
Urine drug screen	X											X
Pregnancy Test[d] (hCG)	X					X			X		X	X
…												
Contact IRT	X	X				X	X	X	X		X	X
Dispense study medication			X[g]			X[g]	X[g]	X[g]	X[g]			X
Return unused study medication						X	X	X	X		X	X

Table 5–1: Schedule of Assessments

Assessment	Screening Period (+1 day)	Rand (+3 days)	Titration Period[a] (±1 day)		EOT/ SOM	Maintenance Period[a] (±2 days)			Taper Period (4 days)[a]		Safety Follow-Up[a] (30 ±5 days)	Un-scheduled Visit[b]
									End of Maintenance[a]/ WD Visit	End of Taper		
		Telemedicine Calls					Telemedicine Calls			Telemedicine Call		
	V1	V2/BL	V3	V4	V5	V6	V7	V8	V9	V10		
	Day -28 to Day -1	Day 0	Day 1	Day 8	Day 15	Day 22	Day 50	Day 78	Day 106	Day 110		

BL=Baseline; BMI=body mass index; CGI=Clinical Global Impressions; C-SSRS=Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; eCRF=electronic Case Report form; EOT=End of Titration; hCG=human chorionic gonadotropin; IRLS=International Restless Legs Scale; IRT=interactive response technology; mMIDI=Modified Minnesota Impulsive Disorder Interview; PK=pharmacokinetic; Rand=randomization; RLS=Restless Legs Syndrome; SOM=Start of Maintenance; V=Visit; WD=withdrawal

Note: Informed consent must be obtained prior to Screening assessments and study-specific procedures.

Note: Rescreening is allowed with the permission of the Study Physician or representation.

Note: For Visit 2, there is a visit window of +3 days to allow for direct-to-subject shipment of study medication. Visit 3/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 3/Day 1.

Note: Visit 6 is the end of the Titration Period and start of the Maintenance Period. Visit 9 is the end of the Maintenance Period and start of the Taper Period.

Note: All visits are via telemedicine calls, with the exception of Visit 1, Visit 6, Visit 9, and SFU. Unscheduled visits are at the discretion of the investigator and may be telemedicine calls.

[a] The visit window for Titration Visits is ±1 day per visit relative to Visit 3 (day of first dose). The visit window for visits during the Maintenance Period, including the End of Maintenance Visit, is ±2 days per visit. The Taper Period, which will last up to a maximum of 4 days, will start on the day after the End of Maintenance Visit. The visit window for Safety Follow-Up Period is 30 days±5 days relative to the end of the Taper Period. Following dose de-escalation, subjects may be eligible to participate in the open-label, long-term follow-up study (RL0007) at any time prior to the Safety Follow-Up Visit (see Section 5). The Safety Follow-Up Visit is for subjects not entering RL0007.

[b] Assessments to be performed are at the investigator's discretion.

[c] C-SSRS is required if the Unscheduled Visit is conducted due to safety or efficacy reasons.

[d] Pregnancy test and menstrual function for all female subjects; serum pregnancy test at Screening and urine pregnancy test at all other visits. A positive urine pregnancy test must be confirmed by a serum pregnancy test.

[e] At the time of PK sampling, sampling time, time of application of study medication, and application site of study medication should be recorded in the eCRF.

[f] At Baseline, subjects must score ≥15 on the IRLS Rating Scale (indicating moderate-to-severe RLS) and must score ≥4 points on the CGI Item 1.

[g] Study medication to be shipped to subject's home to be available no later than this date.

Change #7

Section 6.1, Inclusion Criteria
Inclusion criterion #5 has been removed.

5. Subject's BMI is less than the 95th percentile for his or her age, according to Child and Teen BMI calculator at www.cdc.gov/healthyweight/assessing/bmi/.

Change #8

Section 6.1, Inclusion Criteria, criterion #10

10. If subject is receiving supplemental iron, subject has been on a stable dose for at least 3 months prior to Screening.

Has been changed to:

10a. Subjects who are receiving supplemental iron have been on a stable dose for at least 1 month prior to Screening. Subjects previously treated with supplemental iron must have a washout period of at least 1 month prior to Screening. No supplemental iron administration or iron dose adjustment will be allowed while in study, unless medically necessary.

Change #9

Section 6.2, Exclusion Criteria, criterion #5

4. Subject has a serum ferritin level <50ng/mL at Visit 1/Screening.

Has been changed to:

4a. Subject has a serum ferritin level below the lower limit of normal at Visit 1/Screening.

Change #10

Section 6.2, Exclusion Criteria

Exclusion criteria #13, #14, and #15 were added.

13. Subject has secondary RLS (eg, due to renal insufficiency [uremia], iron deficiency, or rheumatoid arthritis).
14. Subject has a lifetime history of suicide attempts (including actual attempt, interrupted attempt, or aborted attempt), or had suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 at the C-SSRS at Screening (Visit 1).
15. Subject is taking a prohibited concomitant medication (see Section 7.8.2). Prohibited concomitant medication must be discontinued at least 2 weeks prior to Screening (Visit 1).

Change #11

Section 7.1, Description of investigational medicinal products

Table 7-1: Investigational medicinal product

International Non-Proprietary Name	Rotigotine	
Dosage form	Silicone patch containing rotigotine in an adhesive matrix	
Content	Nominal Dose (mg/24h)	Patch size (cm^2)
	1	5
	2	10
Supplier	UCB BIOSCIENCES GmbH Germany	

Has been changed to:

Table 7-1: Investigational medicinal product

International Non-Proprietary Name	Rotigotine	
Dosage form	Silicone patch containing rotigotine in an adhesive matrix	
Content	Nominal Dose (mg/24h)	Patch size (cm^2)
	1	5
	2	10

Change #12

Section 7.2.2, Application instructions

Bullet #3

- The patch should be worn continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately.

Has been changed to:

- The patch should be worn continuously for 24 hours. After 24 hours, the patch should be removed and a new one applied immediately. The WMP app on the study smartphone provides a reminder to place patches at a subject's prespecified time each day (see Section 5 for an overview).

Change #13

Section 7.2.2, Application instructions

Bullet #5

- Each patch should be applied to a different place on the skin each day, for example, from the right side to the left side and from the upper body to the lower body. The patch should not be applied to the same application site more than once every 14 days.

Has been changed to:

- Each patch should be applied to a different place on the skin each day, for example, from the right side to the left side and from the upper body to the lower body. The patch should not be applied to the same application site more than once every 14 days. The WMP app on the study smartphone provides a body map to record daily patch location and a visual reminder of where patches have been placed over the past 14 days (see Section 5 for an overview).

Change #14

Section 7.2.4, General instructions

Bullet #1

- Contact with water while bathing, showering, swimming will not change the way that rotigotine works; however, these activities could loosen the patch. If a patch falls off, re-apply a new patch for the remainder of the day. A new patch should be applied the next day on the subject's regular schedule.

Has been changed to:

- Contact with water while bathing, showering, swimming will not change the way that rotigotine works; however, these activities could loosen the patch. If a patch falls off, re-apply a new patch for the remainder of the day. A new patch should be applied the next day on the subject's regular schedule. The location of a replacement patch can be recorded in the WMP app on the study smartphone (see Section 5 for an overview).

Change #15

Section 8.1, Screening Period

The following paragraph was added:

Subjects who have been screened but not randomized may be rescreened with the permission of the Study Physician or representative.

Change #16

Section 8.1.1, Visit 1 (Day -28 to Day -1)

Assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections listed below, subjects/legal representatives will either visit their local Patient Service Center or mobile study personnel will be sent to the subject's/legal representative's home for sample collections. Samples will be prepared and sent to the central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests (rescreening is allowed with the permission of the medical monitor)
- Urine drug screen

- Urine pregnancy test for all female subjects
- Hormone status

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- eC-SSRS (Screening version)
- IRLS
- CGI
- mMIDI

Has been changed to:

Assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections listed below, mobile study personnel will be sent to the subject's/legal representative's home for sample collections. Samples will be prepared and sent to the central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine drug screen
- Serum pregnancy test for all female subjects
- Hormone status

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Baseline/Screening version)
- IRLS
- CGI
- mMIDI

Change #17

Section 8.2, Titration Period

The visit window for Titration Visits is ±1 day per visit relative to Visit 2/Baseline.

Has been changed to:

The visit window for Titration Visits is ±1 day per visit relative to Visit 3 (Day 1).

Change #18

Section 8.2.1, Visit 2 (Baseline)

Additional assessments and procedures are listed below.

- Recording of medication and procedures. Medications and procedures will be reviewed with the subject/legal representative by the investigator/designated study staff via a telephone or telemedicine call and noted as part of the subject's study record.
- AE assessment. All AEs will be assessed and reviewed throughout the study.
- Contact IRT. Once eligibility is confirmed (see above), the IRT will be contacted to obtain the assigned randomization number and study medication kit numbers for the Titration Period.
- Dispense study medication. Once randomization is completed, study medication for the Titration Period will be distributed. See Section 7.5 for a description of the direct-to-subject shipment process for the remote study model.

Has been changed to:

Additional assessments and procedures are listed below.

- Recording of medication and procedures. Medications and procedures will be reviewed with the subject/legal representative by the investigator/designated study staff via a telephone or telemedicine call and noted as part of the subject's study record.
- AE assessment. All AEs will be assessed and reviewed throughout the study.
- Contact IRT. Once eligibility is confirmed (see above), the IRT will be contacted to obtain the assigned randomization number and study medication kit numbers for the Titration Period.
- Once randomization is completed, study medication for the Titration Period will be assigned and shipped to the subject/legal representatives home for receipt on Day 1. See Section 7.5 for a description of the direct-to-subject shipment process for the remote study model.

Change #19

The following sentence was moved from Section 8.2.1, Visit 2 (Baseline) to Section 8.2.2, Visit 3 (Day 1).

The subject will apply their first patch during the visit under the supervision of the investigator (or designee) via a telemedicine call.

Change #20

Section 8.3.1, Visit 6 (Day 22)

For lab collections and procedures listed below, subjects/legal representatives will either visit their local Patient Service Center or mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Vital signs
- Body weight, height, and BMI
- Safety laboratory tests
- Urine pregnancy test for all female subjects
- PK sampling–record sampling time, time of application of study medication, and application site of study medication in eCRF

Has been changed to:

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Vital signs
- Body weight, height, and BMI
- Safety laboratory tests
- Urine pregnancy test for all female subjects
- PK sampling–record sampling time, time of application of study medication, and application site of study medication in eCRF

Change #21

Section 8.3.2, Visit 7 (Day 50) ad Visit 8 (Day 78)

The following bullets were added to the list of additional assessments and procedures:

- Contact IRT. The IRT will be contacted to obtain study medication kit assignments.
- Dispense study medication. Study medication for the Maintenance Period will be distributed. See Section 7.5 for a description of the direct-to-subject shipment process for the remote study model.

Change #22

Section 8.3.3, Visit 9 (Day 106)/End of Maintenance

Assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, subjects/legal representatives will either visit their local Patient Service Center or mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine pregnancy test for all female subjects
- Hormone status
- PK sampling–record sampling time, time of application of study medication, and application site of study medication in eCRF

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- eC-SSRS (Since Last Visit version)
- IRLS
- CGI
- RLS-6
- mMIDI
- Subject Quality of Life Questionnaire

Additional assessments and procedures are listed below.

- Recording of medication and procedures: See Section 8.2.1.
- AE assessment: See Section 8.2.1.
- Contact IRT: The IRT will be contacted to obtain study medication kit numbers for the Taper Period.
- Dispense study medication (Taper Period de-escalation study medication will be dispensed at this visit). Study medication for the Taper Period will be distributed. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return any unused study medication

Has been changed to:

Assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine pregnancy test for all female subjects

- Hormone status
- PK sampling–record sampling time, time of application of study medication, and application site of study medication in eCRF

Assessments listed below will be completed either by the subject or investigator/trained study staff, as required. Assessments that require interviews will be completed via a telephone or telemedicine call.

- C-SSRS (Since Last Visit version)
- IRLS
- CGI
- RLS-6
- mMIDI
- Subject Quality of Life Questionnaire

Additional assessments and procedures are listed below.

- Recording of medication and procedures: See Section 8.2.1.
- AE assessment: See Section 8.2.1.
- Contact IRT: The IRT will be contacted to obtain study medication kit numbers for the Taper Period.
- Dispense study medication for the Taper Period. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return any unused study medication.

Change #23

Section 8.5, Safety Follow-Up Visit (if applicable)

The assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, subjects/legal representatives will either visit their local Patient Service Center or mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine pregnancy test for all female subjects
- Hormone status

Has been changed to:

The assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Safety laboratory tests
- Urine pregnancy test for all female subjects
- Hormone status

Change #24

Section 8.7, Unscheduled Visit

The assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination
- 12-lead ECG

For lab collections listed below, subjects/legal representatives will either visit their local Patient Service Center or mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Vital signs
- Safety laboratory tests
- Urine pregnancy test for all female subjects
- Hormone status

Has been changed to:

The assessments listed below will be completed by mobile study personnel at the subject's/legal representative's home and records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination, including body weight, height, BMI, and vital signs
- Neurological examination

- 12-lead ECG

For lab collections and procedures listed below, mobile study personnel will be sent to the subject's/legal representative's home. Samples will be prepared and sent to a central laboratory for processing and analysis, and results will be provided to the study site.

- Vital signs
- Safety laboratory tests
- Urine drug screen
- Urine pregnancy test for all female subjects
- Hormone status

Change #25

Section 9.1, International Restless Legs Rating Scale (IRLS)

The IRLS will be performed at Screening, Baseline (Visit 2), and subsequent visits through Visit 8. The IRLS should also be performed in the event that a subject is prematurely withdrawn from the study (Withdrawal Visit).

Has been changed to:

The IRLS will be performed at Screening, Baseline (Visit 2), Visit 6, Visit 7, Visit 8, and Visit 9. The IRLS should also be performed in the event that a subject is prematurely withdrawn from the study (Withdrawal Visit).

Change #26

Section 11.6, Laboratory measurements

Table 11-2: Laboratory measurements

Hematology	Endocrine	Urinalysis
Red blood cell count	Estradiol[a]	Color
Hematocrit	FSH	Appearance
Hemoglobin	IGF-1	Glucose
Platelet count	LH	Protein
White blood cell count[b]	Progesterone[a]	Blood
	Prolactin	Ketones
	Testosterone[c]	Urine pregnancy test[a]
	T3	
	T4	
	TSH	
Chemistry		
ALT	Glucose	
AST	Phosphorus	
Albumin	LDH	
Alkaline phosphatase	Potassium	
Bicarbonate	Serum iron	
BUN	Sodium	
Calcium	Total cholesterol	
Chloride	Total bilirubin	
Creatinine	Total protein	
Ferritin	Transferrin	
GGT	Uric acid	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; IGF-1=insulin-like growth factor-1; LDH=lactate dehydrogenase; LH=luteinizing hormone; T3= triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone

[a] Females only

[b] With differential

[c] Males only

Has been changed to:

Table 11-2: Laboratory measurements

Hematology	Endocrine	Urinalysis
Red blood cell count	Estradiol[a]	Color
Hematocrit	FSH	Appearance
Hemoglobin	IGF-1	Glucose
Platelet count	LH	Protein
White blood cell count[b]	Progesterone[a]	Blood
RBC indices MCH MCV MCHC RDW	Prolactin	Ketones
	Testosterone[c]	Pregnancy test[a]
	T3	
	T4	
	TSH	
Chemistry		
ALT	Glucose	
AST	Phosphorus	
Albumin	LDH	
Alkaline phosphatase	Potassium	
Bicarbonate	Serum iron	
BUN	Sodium	
Calcium	Total cholesterol	
Chloride	Total bilirubin	
Creatinine	Total protein	
Ferritin	Transferrin	
GGT	Uric acid	

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma-glutamyl transferase; IGF-1=insulin-like growth factor-1; LDH=lactate dehydrogenase; LH=luteinizing hormone; MCH=mean corpuscular hemoglobin; MCHC= mean corpuscular hemoglobin concentration; MCV=mean cell volume; RBC=red blood cell; RDW=red cell distribution width; T3= triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone

[a] Females only. Serum pregnancy test at Screening and urine pregnancy test at all other visits. A positive urine pregnancy test must be confirmed by a serum pregnancy test.

[b] With differential.

[c] Males only.

17.2 Protocol Amendment 2

Rationale for the amendment

The protocol has been amended for the following reasons:

- Change the sponsor company name from “UCB Biopharma SPRL” to “UCB Biopharma SRL” since the name of the legal form of the entity UCB Biopharma has changed into “société à responsabilité limitée” abbreviated “SRL”.

17.3 Protocol Amendment 3

Rationale for the amendment

The main purpose of this amendment was to change the shipment of study medication and all required supplies from the study site to the study site's depot/pharmacy.

Other changes included in this amendment are as follows:

- Principal Investigator and Sponsor contact information has been updated.
- Changed Network Oriented Research Assistant (NORA®) to Science 37 Platform (PLATFORM).
- Clarified that the Baseline for the other safety variables is Visit 1.

Modifications and changes

Global changes

The following changes have been made throughout the protocol:

- Changed Network Oriented Research Assistant (NORA®) to Science 37 Platform (PLATFORM) throughout the protocol.

Specific changes

Change #1

STUDY CONTACT INFORMATION:

Sponsor

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Principal/Coordinating Investigator

Name:	David Kudrow, [redacted]
Affiliation:	Science 37
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Phone:	[redacted]

Sponsor Study Physician

Name:	[redacted]
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Email:	[redacted]

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biosciences Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 USA
Phone:	[redacted]
Email:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
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Phone:	[redacted]
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Has been changed to:

Sponsor

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Principal/Coordinating Investigator

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Sponsor Study Physician

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Clinical Project Manager

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Clinical Trial Biostatistician

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Change #2

Section 4.2.2, Other safety variables

- Changes from Baseline in 12-lead ECGs
- Changes from Baseline in vital signs (including assessment of orthostasis)
- Changes from Baseline in laboratory data (hematology, blood chemistry, and urinalysis)
- Changes from Baseline in hormone status

- Changes from Screening in body weight, height, and BMI
- Changes from Baseline in mMIDI
- Changes in menstrual function for all female subjects

Has been changed to:

- Changes from Baseline (Visit 1) in 12-lead ECGs
- Changes from Baseline (Visit 1) in vital signs (including assessment of orthostasis)
- Changes from Baseline (Visit 1) in laboratory data (hematology, blood chemistry, and urinalysis)
- Changes from Baseline (Visit 1) in hormone status
- Changes from Baseline (Visit 1) in body weight, height, and BMI
- Changes in mMIDI
- Changes in menstrual function for all female subjects

Change #3

Section 5.1, Study description

Fourth paragraph

The study will begin with a Screening Period of at least 7 days (maximum of 28 days) prior to Visit 2/Baseline to ensure homogeneous baseline conditions can be established for all subjects. Subjects with prior intake of any dopamine agonists must discontinue the therapy at least 14 days prior to Visit 2/Baseline. Subjects taking L-dopa must discontinue the therapy at least 7 days prior to Visit 2/Baseline. Discontinuation of therapy must be driven by the subject's medical need and not undertaken for the purpose of making a potential subject eligible for the study.

Has been changed to:

The study will begin with a Screening Period of at least 7 days (maximum of 28 days) prior to Visit 2/Baseline to ensure homogeneous baseline conditions can be established for all subjects. Subjects with prior intake of any dopamine agonists or taking L-dopa must discontinue the therapy at least 7 days prior to Visit 2/Baseline. Discontinuation of therapy must be driven by the subject's medical need and not undertaken for the purpose of making a potential subject eligible for the study.

Change #4

Section 7.5, Handling and storage requirements

First and fourth paragraphs

Rotigotine transdermal patches should be stored in the original pouch. Rotigotine should be stored according to the labeling on the clinical trial supply packaging. The investigator (or designee) is responsible for the safe and proper storage of rotigotine at the site. Rotigotine stored by the investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

As part of the remote study model, the study site will provide study medication and all required supplies via direct-to-subject shipments. Once eligibility is confirmed, the study site will contact the interactive response technology (IRT) for randomization assignment, and shipments will be prepared and sent out for delivery to the subject's/legal representative's home/preferred address. Shipments will be confirmed as delivered by the study staff, with appropriate documentation in the subject's study records. The study medication will be confirmed as received in good condition and within the acceptable temperature range (ie, fit for use). A telemedicine call will be completed to instruct the subject/legal representative on the correct storage and administration of the study medication, which will also be documented as part of subject's study record.

Has been changed to:

Rotigotine transdermal patches should be stored in the original pouch. Rotigotine should be stored according to the labeling on the clinical trial supply packaging. The investigator (or designee) is responsible for the safe and proper storage of rotigotine at the site. Rotigotine stored by the investigator (or designee) is to be kept in a secured area with limited access according to the storage conditions mentioned on the label.

As part of the remote study model, the study site's depot/pharmacy will provide study medication and all required supplies via direct-to-subject shipments. Once eligibility is confirmed, the study site will contact the interactive response technology (IRT) for randomization assignment, and shipments will be prepared and sent out for delivery to the subject's/legal representative's home/preferred address. Shipments will be confirmed as delivered by the study staff, with appropriate documentation in the subject's study records. The study medication will be confirmed as received in good condition and within the acceptable temperature range (ie, fit for use). A telemedicine call will be completed to instruct the subject/legal representative on the correct storage and administration of the study medication, which will also be documented as part of subject's study record.

Change #5

Section 7.6, Drug accountability

First and third paragraphs

At the designated timepoints during the study, subjects/legal representatives will return to the study site the unused study medication patches remaining as part of the medication kits, along with the kit itself, via the return shipment materials provided. A Drug Accountability form will be used to record IMP dispensing and return information on a by subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and drug accountability documentation must be made available throughout the study for UCB (or designee) to review.

The investigator may assign some of the investigator's duties for drug accountability at the study site to an appropriate designee.

Has been changed to:

At the designated timepoints during the study, subjects/legal representatives will return to the study site's depot/pharmacy the unused study medication patches remaining as part of the medication kits, along with the kit itself, via the return shipment materials provided. A Drug

Accountability form will be used to record IMP dispensing and return information on a by subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, disposed of at the study site's depot/pharmacy, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and drug accountability documentation must be made available throughout the study for UCB (or designee) to review.

The investigator may assign some of the investigator's duties for drug accountability at the study site's depot/pharmacy to an appropriate designee.

Change #6

Section 7.7, Procedures for monitoring subject compliance

First paragraph

At the designated visits (see Table 5–1), subjects/legal representatives will return all unused IMP and empty IMP containers, using the return shipment supplies provided to them by the study staff. Upon receipt of the returned medication at the study site, the designated study staff will review drug accountability with the subject/legal representative via a telephone or a telemedicine call in order to obtain explanations regarding any discrepancies in compliance with the dosing regimen.

Has been changed to:

At the designated visits (see Table 5–1), subjects/legal representatives will return all unused IMP and empty IMP containers, using the return shipment supplies provided to them by the study staff. Upon receipt of the returned medication at the study site's depot/pharmacy, the designated study staff will review drug accountability with the subject/legal representative via a telephone or a telemedicine call in order to obtain explanations regarding any discrepancies in compliance with the dosing regimen.

18 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

19 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

Approval Signatures

Name: sp1006-protocol-amend-3

Version: 1.0

Document Number: CLIN-000173862

Title: SP1006 Protocol Amendment 3 - Phase 3 Placebo-Controlled Double-Blind

Approved Date: 03 May 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 30-Apr-2021 17:43:07 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 30-Apr-2021 19:17:59 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 03-May-2021 19:58:16 GMT+0000