PROTOCOL RL0007

PROTOCOL RL0007 AMENDMENT 2

A REMOTE, OPEN-LABEL, LONG-TERM FOLLOW-UP STUDY TO DETERMINE THE SAFETY, TOLERABILITY, AND EFFICACY OF ROTIGOTINE TRANSDERMAL SYSTEM AS MONOTHERAPY IN ADOLESCENTS WITH RESTLESS LEGS SYNDROME

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

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LIST OF ABBREVIATIONS

AE	adverse event
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
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
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
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
LTFU	long-term follow-up
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
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
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SFU	Safety Follow-Up
SOC	system organ class
SOP	Standard Operating Procedure
SS	Safety Set
ULN	upper limit of normal

1 SUMMARY

This is a Phase 3, remote, open-label, long-term follow-up (LTFU) study of monotherapy administration of rotigotine transdermal patch in adolescent subjects with idiopathic Restless Legs Syndrome (RLS).

The total study duration per subject will be approximately 14 months after study entry or until the investigational product development is stopped by the Sponsor. The study will include a Titration Period of up to 3 weeks (at maximum), a Maintenance Period of up to 1 year, a Taper Period up to a maximum of 4 days (de-escalation of study medication), and a 30-day Safety Follow-Up (SFU) Period.

During the Titration Period, the investigator should determine whether the subject has reached his/her optimal dose (with a maximum dose of 3mg/24h) prior to completing the scheduled assessments for that visit. Subjects who have reached their optimal dose will maintain that dose and complete the Titration Period without titrating to the next higher dose.

Up to 138 subjects are planned to be treated during the study, assuming that all subjects had tolerated the first dose level of rotigotine in the previous study in adolescent subjects with idiopathic RLS (eg, SP1006) and choose to rollover into the present study (RL0007). A single remote site in the USA is planned to be included in the study. The remote study model to be used in this study 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 assess the long-term safety and tolerability of rotigotine treatment in adolescents with idiopathic RLS. The secondary objective of this study is to assess the long-term efficacy of rotigotine treatment in adolescents with idiopathic RLS.

Primary safety variables include adverse events (AEs) and withdrawals due to AEs. Other safety variables include changes from Baseline in the following: 12-lead electrocardiograms (ECGs), vital signs, hormone status, laboratory tests (hematology, clinical chemistry, and urinalysis), menstrual function, modified Minnesota Impulsive Disorders Interview (mMIDI), body weight, height, and body mass index (BMI).

Efficacy variables include changes from Baseline in the following: International Restless Legs Rating Scale (IRLS) sum score, Clinical Global Impressions (CGI) Item 1 score; and RLS-6 Rating Scales. All statistical analyses of the efficacy variables will be considered exploratory.

Other variables include the Subject Quality of Life and plasma concentrations of rotigotine.

Baseline values from SP1006 will serve as Baseline in RL0007.

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 safety, tolerability, and efficacy 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 (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 assess the long-term safety and tolerability of rotigotine treatment in adolescents with idiopathic RLS.

The secondary objective of this study is to assess the long-term efficacy of rotigotine treatment in adolescents with idiopathic RLS.

4 STUDY VARIABLES

Baseline values from SP1006 will serve as Baseline in RL0007. Baseline values for the other safety variables were collected at Visit 1 of SP1006.

4.1 Safety variables

4.1.1 Primary safety variables

- Occurrence of treatment-emergent adverse events (TEAEs)
- Treatment-emergent adverse events leading to permanent withdrawal of study medication

4.1.2 Other safety variables

- Changes from Baseline (Visit 1, SP1006) in 12-lead ECGs
- Changes from Baseline (Visit 1, SP1006) in vital signs (including assessment of orthostasis)
- Changes from Baseline (Visit 1, SP1006) in hormone status
- Changes from Baseline (Visit 1, SP1006) in laboratory data (hematology, clinical chemistry, and urinalysis)
- Changes from Baseline in menstrual function for all female subjects
- Changes in mMIDI
- Changes from Baseline (Visit 1, SP1006) in body weight, height, and BMI

4.2 Efficacy variables

4.2.1 Secondary efficacy variables

- Changes from Baseline in IRLS sum score at Visit 9
- Changes from Baseline in CGI Item 1 at Visit 9
- Changes from Baseline in RLS-6 at Visit 9

There are no primary efficacy variables.

4.2.2 Other efficacy variables

- Changes from Baseline in IRLS sum score at all visits except Visit 9
- Changes from Baseline in CGI Item 1 at all visits except Visit 9
- Changes from Baseline in RLS-6 at all visits except Visit 9

4.3 Other variables

- Plasma concentrations of rotigotine
- Subject Quality of Life Questionnaire

5 STUDY DESIGN

5.1 Study description

This is a Phase 3, remote, open-label, LTFU study of monotherapy administration of the rotigotine transdermal system. Subjects entering this study from the previous rotigotine study in adolescents (SP1006) must have tolerated the first dose level of rotigotine in that study without meeting the withdrawal criteria.

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). Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

The study will begin with a Titration Period of 3 weeks with the aim of achieving the individually optimized dosage. During the Titration Period, investigators should determine at each visit whether the subject has reached his or her optimal dose prior to completing the scheduled assessments. Once subjects have reached their optimal dose, they will maintain that dose and complete the Titration Period without titrating to the next higher dose.

Titration will be followed by a Maintenance Period of up to 1 year. Dose adjustment of rotigotine is allowed at any time during the Maintenance Period, based on clinical judgment up to a maximum dose of 3mg/24h. At the End of Maintenance (EoM), subjects will enter a 4-day Taper Period followed by a 30-day SFU.

Visits will be scheduled every week during the Titration Period, every 3 months for the Maintenance Period, and at the end of the SFU.

5.1.1 Study duration per subject

The total study duration per subject will be approximately 14 months after study entry or until the investigational product development is stopped by the Sponsor. The study will include a Titration Period of up to 3 weeks (at maximum), a Maintenance Period of up to 1 year, a Taper Period up to a maximum of 4 days (de-escalation of study medication), and a 30-day SFU Period.

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 site

Up to 138 subjects are planned to be treated during the study, assuming that all subjects had tolerated the first dose level of rotigotine in the previous study in adolescent subjects with idiopathic RLS (eg, SP1006) and choose to rollover into the present study (RL0007). A remote clinical study model in the USA is planned to be utilized in the study.

5.1.3 Anticipated regions and countries

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 study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**D90 (M3)**	**D180 (M6)**	**D270 (M9)**	**D360 (M12)**		
Informed consent	X										
Demographics		X									
Eligibility criteria		X									
Withdrawal criteria		X	X	X	X	X	X	X	X		X
Reproductive potential and birth control	X				X	X	X	X	X		
Brief physical examination									X		X
Neurological examination									X		
Telemedicine neurological examination					X	X	X	X		X	X
C-SSRS		X	X	X	X	X	X	X	X	X	X[e]
Vital signs					X	X[f]	X	X[f]	X		X[g]
Body weight, height, and BMI					X		X		X		
12-lead ECG					X				X		X[g]
Safety labs					X		X		X		X[g]
Urine drug screen					X		X		X		
Urine pregnancy test (females) (hCG)					X	X[f]	X	X[f]	X	X	X
Hormone status					X				X		X
PK sampling (blood)					X				X		

Table 5-1: Schedule of study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**D90 (M3)**	**D180 (M6)**	**D270 (M9)**	**D360 (M12)**		
IRLS					X	X	X	X	X		
CGI					X	X	X	X	X		
RLS-6 Rating Scales					X	X	X	X	X		
mMIDI					X	X	X	X	X		X
Menstrual function					X		X		X		
Subject Quality of Life Questionnaire					X	X	X	X	X		
Recording of medication and procedures	X	X	X	X	X	X	X	X	X	X	X[g]
AE assessment	X[h]	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X	X	X	X	X	X	X	X	X	X
Dispense study medication		X[i]			X[i]	X[i]	X[i]	X[i]			X[g]
Return unused study medication			X	X	X	X	X	X	X	X	X[g]

AE=adverse event; BMI=Body Mass Index; CGI=Clinical Global Impressions; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; EoM=End of Maintenance; EoT=End of Taper; hCG=human chorionic gonadotropin; IMP=investigational medicinal product; IRLS=International Restless Legs Rating Scale; IRT=interactive response technology; lab=laboratory; M=Month; mMIDI=modified Minnesota Impulsive Disorder Interview; PK=pharmacokinetic; RLS=Restless Legs Syndrome; SC=Screening; SFU=Safety Follow-Up; SoM=Start of Maintenance; V=Visit; WD=withdrawal

Note: It is preferred that a subject directly continue from SP1006 into RL0007; however, if a subject cannot directly continue into RL0007, the subject has until the SFU Visit of SP1006 to enroll in RL0007.

Note: Visit 1 should occur 4 days prior to Visit 2/Day 1 to allow for direct-to-subject shipment of study medication. Visit 2/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 2/Day 1.

Note: Visit 5 is the end of the Titration Period and start of the Maintenance Period. Visit 9 is the end of the Maintenance Period and the start of the Taper Period.

Table 5-1: Schedule of study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**D90 (M3)**	**D180 (M6)**	**D270 (M9)**	**D360 (M12)**		

Note: The visit window for Screening is ±3 days relative to Day -4. The visit window for Titration Visits is ±3 days relative to Visit 2/Day 1 (day of first dose). The visit window for visits during the Maintenance Period, including the End of Maintenance Visit, is ±14 days relative to Visit 5. The Taper Period, which will last up to a maximum of 4 days, will start after the End of Maintenance Visit (Visit 9). 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.

[a] Subjects who are down-titrated during the Titration Period will automatically enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

[b] All subjects are required to complete the SFU Visit 30 days ±5 days after the final patch removal (end of the Taper Period).

[c] Assessments for Visit 1 of RL0007 should be performed on the same day as the evaluation in the previous rotigotine study (Visit 9 of SP1006).

[d] Taper Period de-escalation study medication will be part of the IMP that will be shipped with Visit 8.

[e] Required if an AE is the reason for the Unscheduled Visit.

[f] May be performed at the subject's/legal representative's home, excluding temperature and respiration rate, by the subject/legal representative if mobile study personnel are not able to be physically present at the home.

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

[h] From Visit 10 of SP1006, if available. If not available from Visit 10 of SP1006, should be collected within 2 weeks of that visit in SP1006.

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

5.3 Rationale for study design and selection of dose

This study will gather data on the long-term safety, tolerability, and efficacy of rotigotine transdermal system in adolescents with idiopathic RLS, allowing subjects from a prior study of rotigotine in adolescents with RLS (SP1006) to continue to receive rotigotine for approximately 13 months. The safety and efficacy data collected in this study are expected to provide valuable information on rotigotine treatment of adolescents with RLS and support fulfillment of the Pediatric Research Equity Act requirements associated with development of rotigotine in the RLS indication.

Restless Legs Syndrome has a prevalence of about 2% in the pediatric population, with 25% of affected children and 50% of affected teenagers reporting moderate to severe symptoms (Pichietti et al, 2007). The etiology of RLS in children is currently poorly understood and diagnosis in young children (<13 years old) may be especially challenging due to their relative inability to describe typical RLS symptoms or because symptoms may not be manifest at young ages (Simakajornboon et al, 2009). Dopaminergic agents are the first choice treatment for RLS in adults; however, to date, no treatment for RLS has been approved for children. Although there is limited information on dopaminergic medications in children, small published reports suggest the effectiveness of dopamine agonists in the management of RLS in children (Simakajornboon et al, 2009). Rotigotine, a D3/D2/D1 receptor agonist, has been approved for the treatment of RLS symptoms in adults in the EU and in the US. Adolescents with RLS may benefit from treatment with rotigotine and administration as a patch formulation may increase the acceptance of medication in this group of subjects.

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)-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 all questionnaires and diaries), visit schedule, or medication intake according to the judgment of the investigator.
3. Subject weighs ≥40kg.
4. Subject has completed at least one dose step in SP1006, a previous study of rotigotine in adolescents with RLS, without meeting withdrawal criteria.
5. 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 drug.
6. Subject is expected to benefit from participation, in the opinion of the investigator.

6.2 Exclusion criteria

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

1. Subject is experiencing an ongoing serious AE (SAE) that is assessed to be related to rotigotine by the investigator or Sponsor.

2a. 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 Columbia-Suicide Severity Rating Scale (C-SSRS) at the final evaluation visit of the previous rotigotine study (ie, Visit 9 of SP1006).

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 an illness 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. Subject takes prohibited concomitant medications as defined in this protocol.
4. Subject or parent(s)/legal representative withdraws his/her consent.
5. The investigator feels that it is in the subject's best interest to be withdrawn.
6. Subject is unwilling to manage the application and removal of patches at any time during the study.
7. The subject develops clinically relevant symptomatic orthostatic hypotension.
8. 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.
9. The subject has a QTc interval ≥500ms or a QTc interval which has increased by ≥60ms as compared to the QTc interval taken at Baseline of SP1006 (Visit 2/Day 0) of the subject's previous study. Bazett's method must be used for correction of QT intervals.
10. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
11. The Sponsor or a regulatory agency requests withdrawal of the subject.
12. 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 staff should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered lost to follow up, the investigator/designated 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 electronic Case Report form (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%).

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 TREATMENT

7.1 Description of investigational medicinal product

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
	3	15
Supplier	UCB Clinical Trial Supply Group	

7.2 Treatments to be administered

7.2.1 Titration Period

The study will begin with a Titration Period of up to 3 weeks (at maximum) with the aim of achieving the individually optimized dosage (with a maximum dose of 3mg/24h).

Subjects will be treated at Visit 1 using the following dose titration schedule until their optimal dose is reached (Table 7–2).

Table 7–2: Dose titration schedule until optimal dose is reached

Visit/Day	**Dose**
Visit 2/Day 1	1mg/24h
Visit 3/Day 8	2mg/24h
Visit 4/Day 15	3mg/24h

During the Titration Period, the investigator should determine whether the subject has reached his/her optimal dose prior to completing the scheduled assessments for that visit. Subjects who have reached their optimal dose should continue at that dose and remain in the Titration Period until they have reached Visit 5 and enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

The optimal dose for each subject will be defined as absence of or maximal reduction in RLS symptoms without intolerable side effects. If the investigator judges that the subject is likely to benefit from a dose increase, then dose titration should continue. If the investigator judges that the subject is unlikely to benefit from a dose increase, then the dose is defined as optimal.

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 down-titrated to their previous dose level and continue at that dose until they reach Visit 5 and enter the Maintenance Period.

7.2.2 Maintenance Period

Titration will be followed by a Maintenance Period of up to 1 year. Dose adjustment of rotigotine is allowed at any time during the Maintenance Period, based on clinical judgment, up

to a maximum dose of 3mg/24h. 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 SFU Period.

7.2.3 Taper Period

After the EoM/Withdrawal Visit, subjects will enter a Taper Period up to a maximum of 4 days. Based on the final maintenance dose, subjects will begin dose de-escalation by 1 dose level every 2 days (Table 7–3).

Table 7–3: Taper de-escalation schedule

Final maintenance dose	Day 1/Day 2	Day 3/Day 4
3mg/24h	2mg/24h	1mg/24h
2mg/24h	1mg/24h	0
1mg/24h	0	0

7.2.4 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/legal representative) 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 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.
- 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/legal representatives) should wash their hands with soap and water immediately after handling the patch.

7.2.5 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/legal representative should tell their investigator.

7.2.6 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.
- 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.
- The parent/legal representative 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 parent/legal representative 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), 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 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 parent/legal representative 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)

No concomitant medications are prohibited during the study.

7.8.3 Rescue medication

Not applicable.

7.9 Blinding

This is an open-label study.

7.10 Randomization and numbering of subjects

To enroll a subject at Visit 1, the investigator (or designee) will call the IRT and provide brief details about the subject to be enrolled. Each subject will maintain their 5-digit subject number assigned at Visit 1 of their previous RLS study (SP1006). The subject number will be required in all communication between the investigator (or designee) and the IRT regarding a particular subject. The investigator (or designee) will be given the kit number to be dispensed to the

subject. The IRT will allocate kit numbers based on subject number during the course of the study. Subject numbers and kit numbers will be tracked via the IRT throughout the study.

8 STUDY PROCEDURES BY VISIT

8.1 Visit 1 (Screening/Day -4)

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 and which complies with regulatory requirements. 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 and parent/legal representative will be given the opportunity to ask the investigator any questions regarding potential risks and benefits of participation in the study.

Assessments for Visit 1 of RL0007 should be performed on the same day as the final evaluation visit of the previous rotigotine study (Visit 9 of SP1006).

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.

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:

- Reproductive potential and birth control

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 study medication kit numbers for the Titration Period.

8.2 Titration Period

The visit window for the Titration Period is ±3 days relative to Visit 2 (day of first dose). The Titration Period starts at Visit 2/Day 1 and ends at Visit 5/Day 22.

8.2.1 Visit 2 (Day 1)

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

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

Additional assessments and procedures are listed below.

- Recording of medication and procedures: See Section 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted.
- Dispense study medication. Study medication for the Titration Period will be shipped to the subject's/legal representative's home/preferred address to be available for the first dose of study medication in RL0007 at Visit 2/Day 1. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.

8.2.2 Visit 3 and Visit 4 (Day 8 and Day 15)

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

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

Additional assessments and procedures are listed below.

- Recording of medication and procedures: See Section 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted.
- Return 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.

8.2.3 Visit 5 (Day 22)

The Titration Period ends at Visit 5.

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

- Withdrawal criteria
- Reproductive potential and birth control
- Menstrual function for all female subjects
- Telemedicine neurological examination

The assessments listed below will be completed by the subject/subject's legal representative's local health provider or mobile study personnel will be sent to the subject's/legal representative's home. Records of the procedures will be obtained, with information noted as part of the subject's study record.

- 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 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 drug screen
- 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 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted to obtain study medication kit numbers for the Maintenance Period.
- Dispense study medication. Study medication for Visit 5 will be shipped to the subject's/legal representative's home/preferred address to be available for that visit. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return unused study medication. See Section 8.2.2.

8.3 Maintenance Period

The Maintenance Period starts at Visit 5 and ends at Visit 9.

8.3.1 Visit 6 (Month 3)

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

- Reproductive potential and birth control
- Telemedicine neurological examination

For lab collections listed below, samples will be collected at home by the subject/legal representative, and results will be provided to the study site.

- Vital signs
- Urine pregnancy test for all female subjects

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 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted.
- Dispense study medication. Study medication for Visit 6 will be shipped to the subject's/legal representative's home/preferred address to be available for that visit. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return unused study medication. See Section 8.2.2.

8.3.2 Visit 7 (Month 6)

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
- Reproductive potential and birth control
- Menstrual function for all female subjects
- Telemedicine neurological examination

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.

- Vital signs
- Body weight, height, and BMI
- Safety laboratory tests
- Urine drug screen
- Urine pregnancy test for all female subjects

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 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted.
- Dispense study medication. Study medication for Visit 7 will be shipped to the subject's/legal representative's home/preferred address to be available for that visit. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return unused study medication. See Section 8.2.2.

8.3.3 Visit 8 (Month 9)

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
- Reproductive potential and birth control
- Telemedicine neurological examination

For lab collections listed below, samples will be collected at home by the subject/legal representative, and results will be provided to the study site.

- Vital signs
- Urine pregnancy test for all female subjects

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 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted.
- Dispense study medication. Study medication for Visit 8 will be shipped to the subject's/legal representative's home/preferred address to be available for that visit. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return unused study medication. See Section 8.2.2.

8.3.4 Visit 9/ End of Maintenance Visit (Month 12)

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
- Reproductive potential and birth control
- Menstrual function for all female subjects

The assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider or mobile study personnel will be sent to the subject's/legal representative's home. Records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination
- Body weight, height, and BMI
- 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
- 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 8.1.
- AE assessment: See Section 8.1.
- Contact IRT: The IRT will be contacted.
- Dispense study medication. Study medication for the Taper Period will be shipped to the subject's/legal representative's home/preferred address to be available by Visit 9. See Section 7.5 for the description of the direct-to-subject shipment process for the remote study model.
- Return unused study medication. See Section 8.2.2.

8.4 Taper Period

The Taper Period, which will last up to a maximum of 4 days, will start after the subject has completed the EoM Visit (Visit 9). Taper Period de-escalation study medication will be part of the IMP that will be shipped with Visit 8.

8.5 Safety Follow-up Visit

The visit window for SFU Period is 30 days ±5 days relative to the end of the Taper Period.

For lab collections listed below, samples will be collected at home by the subject/legal representative, and results will be provided to the study site.

- Urine pregnancy test for all female subjects

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.

- Telemedicine neurological examination
- C-SSRS (Since Last Visit version)

Additional assessments and procedures are listed below.

- Recording of medication and procedures. See Section 8.1.
- AE assessment. See Section 8.1.
- Contact IRT. The IRT is contacted to process the subject's completion of the study.
- Return unused study medication. See Section 8.2.2.

8.6 Withdrawal Visit

Procedures for a withdrawal visit are the same as for the EoM Visit (Visit 9/Month 12).

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 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
- Telemedicine neurological examination
- 12-lead ECG

For lab collections listed below, mobile study personnel may 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 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 8.1.
- AE assessment. See Section 8.1.
- 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 8.2.2.

9 ASSESSMENT OF EFFICACY

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

9.1 International Restless Legs Rating Scale

The IRLS will be performed at Visit 6 and subsequent visits through 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.

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 EoM 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 Visit 6 and subsequent visits 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.

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 Visit 6 and subsequent visits 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 8 and subsequent visits through 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 through 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 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. Adverse events present at Visit 9 for SP1006 will have to be recorded for RL0007 since this is Visit 1 and the start of this study.

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 criteria 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, important medical event].

  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 Investigator 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 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:

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the early discontinuation visit.
- A SFU 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 and should be available in the Investigator Site File. In case of questions about the consent process, the investigator may contact the UCB/contract research organization (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 a serious adverse event (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 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 following laboratory parameters 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
	Prolactin	Ketones
	Testosterone[c]	Urine pregnancy test[a]
	T3	
	T4FR	
	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; T4FR=free thyroxine; TSH=thyroid-stimulating hormone

[a] Females only
[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 11–4 (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]

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)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function

Table 11–5: PDILI information to be collected

New or updated information
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 body systems may be performed when mobile study personnel are present.

The neurological examination may be performed when mobile study personnel are present and may include assessment of mental status, cranial nerves, plantar reflexes, deep tendon reflexes, muscle strength, gait, coordination/balance, involuntary movements, and sensory perception.

The telemedicine neurological examination may include assessment of mental status, gait, and coordination/balance.

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], free thyroxine [T4FR], 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, 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 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.

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 (ink, typing, printing, optical disc). Photocopies and/or printouts of eCRFs are not considered acceptable source documents.

Source documents 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, pharmacy records, care records, ECG or other printouts, completed scales, quality of life questionnaires, or video, 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 files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the CRF 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 in 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 in the subject's medical 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 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 (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 Trial Master File.

12.6 Audit and inspection

The investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic 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/investigational device have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB 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.

13.1 Definition of analysis sets

- Safety Set (SS): all subjects who have at least 1 patch (rotigotine) applied. This analysis set will be used for all analyses.

13.2 General 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 efficacy variables

Summary statistics will be provided for the efficacy variables by final dose or if applicable, the dose most frequently administrated to the subject.

The number of subjects (n), arithmetic mean, standard deviation, median, minimum, and maximum will be provided for all visits for IRLS and RLS-6. Baseline for IRLS and RLS-6 is defined as the last assessment before first dosing in the previous RLS study of rotigotine (SP1006).

Frequency tables will be provided for the CGI Item 1 by visit. Additionally, the changes from Baseline will be tabulated for CGI Item 1 by dose. No imputation rules will be applied.

Baseline for CGI Item 1 is defined as last assessment before first dosing in the previous RLS study of rotigotine (SP1006).

In order to evaluate the impact of total duration of exposure, results for efficacy variables will also be presented by categories of total duration of exposure, including exposure from SP1006.

13.4 Planned safety and other analyses

13.4.1 Safety analyses

All safety data will be analyzed for the SS. In general, Baseline is defined as the last assessment before first dosing in the previous study of rotigotine, SP1006.

Safety variables will be analyzed in a descriptive way. Results will be presented overall.

Individual listings of AEs (age, body height, body weight, race, gender, system organ class [SOC]), and preferred term according to the Medical Dictionary for Regulatory Activities [MedDRA®], AE as reported, start and end with relative days to study medication administration, duration, intensity, seriousness, and relationship to study medication, action taken and final outcome) will be provided. The start and stop of each AE will be given as absolute and relative to the time of patch application. In addition, listings for subjects with SAEs, AEs leading to discontinuation, and other significant AEs will be provided.

The incidence of treatment-emergent AEs will be summarized in frequency tables by actual dose at the start of the event, modal dose, and intensity, ordered by primary SOC, high level term, and PTs. The incidence of drug-related AEs will be described in the same way. Frequency tables for withdrawals due to AEs by last dose and by modal dose will be provided.

13.4.2 Other analyses

Summary statistics will be provided for the laboratory data, menstrual function, mMIDI, vital signs, body weight, height, BMI, ECG, and neurological examination findings.

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

In order to evaluate the impact of total duration of exposure, results for safety variables will also be presented by categories of total duration of exposure. Appropriate categories for duration of exposure are data driven and will be defined during data analysis.

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 key safety 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.

13.6 Handling of dropouts or missing data

In general, data will be analyzed as observed, however for subjects who prematurely withdraw for any reason, data collected during the Withdrawal Visit will be used to impute measurements at the next planned visit.

13.7 Planned interim analysis and data monitoring

Due to the single-arm, open-label design of this study, no formal interim analysis is planned. However, interim database locks may be performed to allow safety and efficacy analyses in support of submission activities or to allow optimization of the development program.

13.8 Determination of sample size

No formal sample size calculation was performed for this study. Initially, a maximum of 138 subjects from a prior study (SP1006) are expected to participate in the current study, based on the assumption that all planned subjects from SP1006 will roll-over into the present study.

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 legal representative). 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 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 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

The study will be conducted under the auspices of an IRB, 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 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 for its review and approval.

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

The investigator will also promptly report to the IRB 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 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 as allowed.

As part of the IRB requirements for continuing review of approved studies, the investigator will be responsible for submitting periodic progress reports to the IRB (based on IRB 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 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 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 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 in previous study SP1006.

The investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB, 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, 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 amendment was to remove visits by the subjects/legal representatives to their local healthcare provider or to national Patient Service Centers for various lab collections and designated study procedures.

Other changes included in this amendment are as follows:

- Sponsor contact information has been updated.
- Clarified primary safety variables and other safety variables.
- Changed the heading Key efficacy variables to Secondary efficacy variables, and clarified that there are no primary efficacy variables.
- Clarified the definition of neurological examination.
- Clarified Titration Period dose titration schedule and entry into Maintenance Period.
- Typographic errors and changes of an editorial nature were made.

Modifications and changes

Global changes

The following change was made throughout the protocol:

- Changed eC-SSRS to C-SSRS

Specific changes

Change #1

Study contact information

Sponsor Study Physician

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Strasse 10, 40789 Monheim, Germany
Phone:	[redacted]
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]
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 Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 USA
Phone:	[redacted]
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]

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

Change #2

Section 1, Summary

During the Titration Period, the investigator should determine whether the subject has reached his/her optimal dose (with a maximum dose of 3mg/24h) prior to completing the scheduled assessments for that visit. Subjects who have reached their optimal dose should proceed to the Maintenance Period (Visit 5) and complete those assessments.

Has been changed to:

During the Titration Period, the investigator should determine whether the subject has reached his/her optimal dose (with a maximum dose of 3mg/24h) prior to completing the scheduled assessments for that visit. Subjects who have reached their optimal dose will maintain that dose and complete the Titration Period without titrating to the next higher dose.

Change #3

Section 2, Introduction

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 Network Oriented Research Assistant (NORA®), which is the backbone of the studies conducted via this model. NORA 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, 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:

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 Network Oriented Research Assistant (NORA®), which is the backbone of the studies conducted via this model. NORA 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.

Change #4

Section 4, Study variables

The following text was added: Baseline values from SP1006 will serve as Baseline in RL0007.

Change #5

Section 4.1.1, Primary safety variables

- AEs
- Withdrawals due to AEs

Has been changed to:

- Occurrence of treatment-emergent adverse events (TEAEs)
- Treatment-emergent adverse events leading to permanent withdrawal of study medication

Change #6

Section 4.1.2, Other safety variables

- Changes from Baseline in body weight, height, and BMI

Has been changed to:

- Changes from Screening in body weight, height, and BMI

Change #7

Section 4.1.2, Key efficacy variables

4.1.2, Key efficacy variables

- Changes from Baseline in IRLS sum score at Visit 9
- Changes from Baseline in CGI Item 1 at Visit 9
- Changes from Baseline in RLS-6 at Visit 9

Has been changed to:

4.1.2, Secondary efficacy variables

- Changes from Baseline in IRLS sum score at Visit 9
- Changes from Baseline in CGI Item 1 at Visit 9
- Changes from Baseline in RLS-6 at Visit 9

There are no primary efficacy variables.

Change #8

Section 5.1, Study design

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. Subjects who are back-titrated during the Titration Period will automatically enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

The study will begin with a Titration Period of up to 3 weeks (at maximum) with the aim of achieving the individually optimized dosage. During the Titration Period, investigators should determine at each visit whether the subject has reached his or her optimal dose prior to completing the scheduled assessments. Once subjects have reached their optimal dose, they should proceed to Maintenance Period (Visit 5) and complete those assessments.

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 will visit subjects'/legal representatives' homes to complete certain study procedures (eg, neurological exams, physical exams, ECGs, lab collections, and vital signs). Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

The study will begin with a Titration Period of 3 weeks with the aim of achieving the individually optimized dosage. During the Titration Period, investigators should determine at each visit whether the subject has reached his or her optimal dose prior to completing the scheduled assessments. Once subjects have reached their optimal dose, they will maintain that dose and complete the Titration Period without titrating to the next higher dose.

Change #9

Section 5.2, Schedule of study activities

Table 5-1: Schedule of study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**M3**	**M6**	**M9**	**M12**		
Informed consent	X										
…											
Return unused study medication			X	X	X	X	X	X	X	X	X[g]

AE=adverse event; BMI=Body Mass Index; CGI=Clinical Global Impressions; D=Day; ECG=electrocardiogram; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; EoM=End of Maintenance; EoT=End of Taper; hCG=human chorionic gonadotropin; IRLS=International Restless Legs Rating Scale; IRT=interactive response technology; lab=laboratory; M=Month; mMIDI=modified Minnesota Impulsive Disorder Interview; PK=pharmacokinetic; RLS=Restless Legs Syndrome; SC=Screening; SFU=Safety Follow-Up; SoM=Start of Maintenance; V=Visit; WD=withdrawal

Note: 1 month=30 days.

Note: It is preferred that a subject directly continue from SP1006 into RL0007; however, if a subject cannot directly continue into RL0007, the subject has until the SFU Visit of SP1006 to enroll in RL0007.

Note: Visit 1 should occur 4 days prior to Visit 2/Day 1 to allow for direct-to-subject shipment of study medication. Visit 2/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 2/Day 1.

Note: Visit 5 is the end of the Titration Period and start of the Maintenance Period. Visit 9 is the end of the Maintenance Period and the start of the Taper Period.

Note: The visit window for Screening is ±3 days relative to Day -4. The visit window for Titration Visits is ±3 days relative to Visit 2/Day 1 (day of first dose). The visit window for visits during the Maintenance Period, including the End of Maintenance Visit, is ±14 days relative to Visit 5. The Taper Period, which will last up to a maximum of 4 days, will start after the End of Maintenance Visit (Visit 9). 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.

[a] Subjects who are back-titrated during the Titration Period will automatically enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

[b] All subjects are required to complete the SFU Visit 30 days ±5 days after the final patch removal (end of the Taper Period).

[c] Assessments for Visit 1 of RL0007 should be performed on the same day as the evaluation in the previous rotigotine study (Visit 9 of SP1006).

[d] Taper Period de-escalation study medication will be shipped to the subject's/legal respresentative's home/preferred address to be available by this visit.

[e] Required if an AE is the reason for the Unscheduled Visit.

[f] May be performed at the subject's/legal representative's home.

Table 5-1: Schedule of study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**M3**	**M6**	**M9**	**M12**		

[g] Assessments to be performed are at the investigator's discretion.
[h] From Visit 10 of SP1006, if available. If not available from Visit 10 of SP1006, should be collected within 2 weeks of that visit in SP1006.
[i] 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 study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**D90 (M3)**	**D180 (M6)**	**D270 (M9)**	**D360 (M12**		
Informed consent	X										
…											
Return unused study medication			X	X	X	X	X	X	X	X	X[g]

AE=adverse event; BMI=Body Mass Index; CGI=Clinical Global Impressions; C-SSRS=Columbia-Suicide Severity Rating Scale; D=Day; ECG=electrocardiogram; EoM=End of Maintenance; EoT=End of Taper; hCG=human chorionic gonadotropin; IMP=investigational medicinal product; IRLS=International Restless Legs Rating Scale; IRT=interactive response technology; lab=laboratory; M=Month; mMIDI=modified Minnesota Impulsive Disorder Interview; PK=pharmacokinetic; RLS=Restless Legs Syndrome; SC=Screening; SFU=Safety Follow-Up; SoM=Start of Maintenance; V=Visit; WD=withdrawal

Note: It is preferred that a subject directly continue from SP1006 into RL0007; however, if a subject cannot directly continue into RL0007, the subject has until the SFU Visit of SP1006 to enroll in RL0007.

Note: Visit 1 should occur 4 days prior to Visit 2/Day 1 to allow for direct-to-subject shipment of study medication. Visit 2/Day 1 is the first day of study medication exposure. All subsequent visits are calculated based on Visit 2/Day 1.

Table 5-1: Schedule of study assessments

	SC (±3 days)	Titration Period[a]				Maintenance Period Year 1[a]				SFU[b] (30±5 days)	Unscheduled Visit
Visit	**V1[c]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9[d]**		
Day/Month	**D-4**	**D1**	**D8**	**D15**	**D22**	**D90 (M3)**	**D180 (M6)**	**D270 (M9)**	**D360 (M12**		

Note: Visit 5 is the end of the Titration Period and start of the Maintenance Period. Visit 9 is the end of the Maintenance Period and the start of the Taper Period.
Note: The visit window for Screening is ±3 days relative to Day -4. The visit window for Titration Visits is ±3 days relative to Visit 2/Day 1 (day of first dose). The visit window for visits during the Maintenance Period, including the End of Maintenance Visit, is ±14 days relative to Visit 5. The Taper Period, which will last up to a maximum of 4 days, will start after the End of Maintenance Visit (Visit 9). 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.

[a] Subjects who are down-titrated during the Titration Period will automatically enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.
[b] All subjects are required to complete the SFU Visit 30 days ±5 days after the final patch removal (end of the Taper Period).
[c] Assessments for Visit 1 of RL0007 should be performed on the same day as the evaluation in the previous rotigotine study (Visit 9 of SP1006).
[d] Taper Period de-escalation study medication will be part of the IMP that will be shipped with Visit 8.
[e] Required if an AE is the reason for the Unscheduled Visit.
[f] May be performed at the subject's/legal representative's home, excluding temperature and respiration rate, by the subject if mobile study personnel are not able to be physically present at the home.
[g] Assessments to be performed are at the investigator's discretion.
[h] From Visit 10 of SP1006, if available. If not available from Visit 10 of SP1006, should be collected within 2 weeks of that visit in SP1006.
[i] Study medication to be shipped to subject's home to be available no later than this date.

Change #10

Section 6.2, Exclusion criterion #2

2. 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 electronic Columbia Suicide Severity Rating Scale (eC-SSRS) at the final evaluation visit of the previous rotigotine study (ie, Visit 10 of SP1006).

Has been changed to:

2a. 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 Columbia-Suicide Severity Rating Scale (C-SSRS) at the final evaluation visit of the previous rotigotine study (ie, Visit 9 of SP1006).

Change #11

Section 7.2.1, Titration Period

Table 7-2: Dose titration schedule until optimal dose is reached

Visit/Day	Dose
Visit 1/Day 1	1mg/24h
Visit 2/Day 8	2mg/24h
Visit 3/Day 15	3mg/24h

During the Titration Period, the investigator should determine whether the subject has reached his/her optimal dose prior to completing the scheduled assessments for that visit. Subjects who have reached their optimal dose should proceed to the Maintenance Period (Visit 5) and complete those assessments. Subjects who are back-titrated during the Titration Period will automatically enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

The optimal dose for each subject will be defined as absence of or maximal reduction in RLS symptoms without intolerable side effects. If the investigator judges that the subject is likely to benefit from a dose increase, then dose titration should continue. If the investigator judges that the subject is unlikely to benefit from a dose increase, then the dose is defined as optimal, and the subject enters 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.

Has been changed to:

Table 7-2: Dose titration schedule until optimal dose is reached

Visit/Day	Dose
Visit 2/Day 1	1mg/24h
Visit 3/Day 8	2mg/24h
Visit 4/Day 15	3mg/24h

During the Titration Period, the investigator should determine whether the subject has reached his/her optimal dose prior to completing the scheduled assessments for that visit. Subjects who have reached their optimal dose should continue at that dose and remain in the Titration Period until they have reached Visit 5 and enter the Maintenance Period. Subjects are allowed to be up-titrated and down-titrated at the discretion of the investigator during the Maintenance Period.

The optimal dose for each subject will be defined as absence of or maximal reduction in RLS symptoms without intolerable side effects. If the investigator judges that the subject is likely to benefit from a dose increase, then dose titration should continue. If the investigator judges that the subject is unlikely to benefit from a dose increase, then the dose is defined as optimal.

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 down-titrated to their previous dose level and continue at that dose until they reach Visit 5 and enter the Maintenance Period.

Change #12

Section 8.2, Titration Period

The visit window for the Titration Period is ±3 days relative to Visit 2 (day of first dose). The Titration Period starts at Visit 2/Day 1 and ends at Visit 5/Day 22 or when the subject reaches his/her optimal dose.

Has been changed to:

The visit window for the Titration Period is ±3 days relative to Visit 2 (day of first dose). The Titration Period starts at Visit 2/Day 1 and ends at Visit 5/Day 22.

Change #13

Section 8.2.3, Visit 5 (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.

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.

Change #14

Section 8.3, Maintenance Period

The Maintenance Period starts at Visit 6 and ends at Visit 9.

Has been changed to:

The Maintenance Period starts at Visit 5 and ends at Visit 9.

Change #15

Section 8.3.1, Visit 6 (Month 3)

For lab collections listed below, subjects/legal representatives will either visit their local Patient Service Center or healthcare practitioner, 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.

- Vital signs (may be performed at the subject's/legal representative's home)
- Urine pregnancy test for all female subjects (may be performed at the subject's/legal representative's home)

Has been changed to:

For lab collections listed below, samples will be collected at home by the subject/legal representative, and results will be provided to the study site.

- Vital signs
- Urine pregnancy test for all female subjects

Change #16

Section 8.3.2, Visit 7 (Month 6)

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.

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.

Change #17

Section 8.3.3, Visit 8 (Month 9)

Lab collections listed below, subjects/legal representatives will either visit their local Patient Service Center or healthcare practitioner, 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.

- Vital signs (may be performed at the subject's/legal representative's home)
- Urine pregnancy test for all female subjects (may be performed at the subject's/legal representative's home)

Has been changed to:

For lab collections listed below, samples will be collected at home by the subject/legal representative, and results will be provided to the study site.

- Vital signs
- Urine pregnancy test for all female subjects

Change #18

Section 8.3.4, Visit 9/End of Maintenance (Month 12)

The assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider or mobile study personnel will be sent to the subject's/legal representative's home. Records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination
- Body weight, height, and BMI
- 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.

Has been changed to:

The assessments listed below will be completed by the subject/subject's/legal representative's local healthcare provider or mobile study personnel will be sent to the subject's/legal

representative's home. Records of the procedures will be obtained, with information noted as part of the subject's study record.

- Brief physical examination
- Body weight, height, and BMI
- Vital signs
- Telemedicine 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.

Change #19

Section 8.4, Taper Period

The Taper Period, which will last up to a maximum of 4 days, will start after the subject has completed the EoM Visit (Visit 9). The de-escalation study medication to be taken during the Taper Period will be shipped for receipt at the subject's/legal representative's home/preferred address by Visit 9.

Has been changed to:

The Taper Period, which will last up to a maximum of 4 days, will start after the subject has completed the EoM Visit (Visit 9). Taper Period de-escalation study medication will be part of the IMP that will be shipped with Visit 8.

Change #20

Section 8.5, Safety Follow-Up Visit

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.

Has been changed to:

For lab collections listed below, samples will be collected at home by the subject/legal representative, and results will be provided to the study site.

Change #21

Section 8.7, Safety Follow-Up Visit

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.

Has been changed to:

For lab collections and procedures listed below, mobile study personnel may 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.

Change #22

Sectoin 9.1, International Restless Legs Rating Scale

The fifth paragraph:

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

Has been changed:

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

Change #23

Sectoin 9.2, Clinical Global Impression

The fourth paragraph has been removed:

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.

Change #24

Section 11.7.3, Physical and neurological examination

A brief physical examination of 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.

Has been changed to:

A brief physical examination of body systems may be performed when mobile study personnel are present.

The neurological examination may be performed when mobile study personnel are present and may include assessment of mental status, cranial nerves, plantar reflexes, deep tendon reflexes, muscle strength, gait, coordination/balance, involuntary movements, and sensory perception.

Change #25

Section 11.6, Laboratory measurements (Table 11-2) and Section 11.7.4, Hormone status

Thyroxine [T4]

Has been changed to:

Free thyroxine [T4FR]

Change #26

Section 11.7.7, Assessment of suicidal ideation and behavior

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

Has been changed to:

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).

Change #27

Section 13.3.1, Analysis of the efficacy variables

The first and fifth paragraphs:

Summary statistics will be provided for the efficacy variables by dose.

In order to evaluate the impact of total duration of exposure, results for efficacy variables will also be presented by categories of total duration of exposure.

Have been changed to:

Summary statistics will be provided for the efficacy variables by final dose or if applicable, the dose most frequently administrated to the subject.

In order to evaluate the impact of total duration of exposure, results for efficacy variables will also be presented by categories of total duration of exposure, including exposure from SP1006.

Change #28

Section 13.6, Handling of dropouts or missing data

In general, data will be analyzed as observed, however for subjects who prematurely withdraw for any reason, data collected during the Withdrawal Visit will be used to impute measurements at the next consecutive visit.

Has been changed to:

In general, data will be analyzed as observed, however for subjects who prematurely withdraw for any reason, data collected during the Withdrawal Visit will be used to impute measurements at the next planned visit.

17.2 Protocol Amendment 2

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 (SP1006).
- Typographic errors were corrected.

Modifications and changes

Global changes

The following change was 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]
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Sponsor Study Physician

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Clinical Project Manager

Name:	[redacted]
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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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Change #2

Section 4, Study variables

Baseline values from SP1006 will serve as Baseline in RL0007.

Has been changed to:

Baseline values from SP1006 will serve as Baseline in RL0007. Baseline values for the other safety variables were collected at Visit 1 of SP1006.

Change #3

Section 4.1.2, Other safety variables

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

Has been changed to:

- Changes from Baseline (Visit 1, SP1006) in 12-lead ECGs
- Changes from Baseline (Visit 1, SP1006) in vital signs (including assessment of orthostasis)
- Changes from Baseline (Visit 1, SP1006) in hormone status
- Changes from Baseline (Visit 1, SP1006) in laboratory data (hematology, clinical chemistry, and urinalysis)
- Changes from Baseline in menstrual function for all female subjects
- Changes in mMIDI
- Changes from Baseline (Visit 1, SP1006) in body weight, height, and BMI

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), 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), 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: rl0007-protocol-amend-2

Version: 1.0

Document Number: CLIN-000173921

Title: RL0007 Protocol Amendment 2 - Phase 3, Open-Label

Approved Date: 03 May 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 30-Apr-2021 17:45:17 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 30-Apr-2021 19:15:43 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 03-May-2021 19:58:50 GMT+0000