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LML134

Clinical Trial Protocol CLML134X2201

A randomized, subject and investigator-blinded, placebo controlled, cross-over, multi-center Proof of Concept (PoC) study to assess the wakefulness promoting effect, safety, tolerability, and pharmacokinetics of LML134 in shift work disorder (SWD) patients

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO& PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

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List of abbreviations

ACR	Albumin-creatinine ratio
AE	adverse event
AHI	apnea-hypopnea index
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	Body Mass Index
BP	blood pressure
BUN	blood urea nitrogen
C-SSRS	Columbia Suicide Severity Rating Scale
CFR	U.S. Code of Federal Regulation
	Corporate Confidential Information
CGI-S	Clinical Global Impression-Severity
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
COA	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSF	cerebrospinal fluid
CV	coefficient of variation
DDE	Direct Data Entry
ECDEU	Early Clinical Drug Evaluation Program
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ES	excessive sleepiness
eSource	Electronic Source
FIH	First-in-human

GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
H3R	H3 receptors
HA	histamine
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HV	healthy volunteers
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notifications
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

LDH	lactate dehydrogenase
LLN	lower limit of normal
LLOQ	lower limit of quantification
MAD	Multiple Ascending Dose
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MSLT	Multiple Sleep Latency Test
NIRT	Novartis Interactive Response Technology
PA	posteroanterior
PCR	Protein-creatinine ratio
PD	pharmacodynamic(s)

PET	positron emission tomography
PK	pharmacokinetic(s)
PLMSArI	periodic leg movement in sleep with arousal index
PoC	Proof of Concept
PoP-PK	Population Pharmacokinetics
PRO	Patient Reported Outcomes
PSG	polysomnography
PT	prothrombin time
QM	Quality Management
QTcF	Fridericia QT correction formula
RBC	red blood cell(s)
REM	rapid eye movement
RO	receptor occupancy
SAD	Single Ascending Dose
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
SWD	shift work disorder
TBL	total bilirubin
tMeHA	tele-methylhistamine
TMN	tuberomammillary nucleus
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
T1/2	The terminal elimination half-life [time]
Tmax	The time to reach the maximum concentration after drug administration [time]
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest

Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

Protocol summary

Protocol number	CLML134X2201
Full Title	A randomized, subject and investigator-blinded, placebo controlled, cross-over, multi-center Proof of Concept (PoC) study to assess the wakefulness promoting effect, safety, tolerability, and pharmacokinetics of LML134 in shift work disorder (SWD) patients
Brief title	A Proof of Concept (PoC) study to assess the wakefulness promoting effect of LML134 in shift work disorder patients
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The main purpose of this study is to demonstrate that LML134 can increase wakefulness compared to placebo in patients with shift work disorder (SWD) measured by objective and subjective endpoints of wakefulness, i.e. the sleep latency in the multiple sleep latency test (MSLT) Safety and PK of LML134 will also be evaluated. Corporate Confidential Information
Primary Objective(s)	To demonstrate that wakefulness in SWD patients is significantly increased after treatment with LML134 compared to placebo
Secondary Objectives	To assess the safety and tolerability of LML134 compared to placebo in SWD patients To assess the plasma pharmacokinetics of LML134 in SWD patients To evaluate the time course of LML134 effect on wakefulness compared to placebo
Study design	This is a randomized, subject and investigator-blinded, placebo controlled, crossover, multi-center Proof of Concept (PoC) study with in-house simulated laboratory night shifts in patients with SWD. This non-confirmatory study will include two treatment arms: LML134 and placebo. After a screening period, the treatment phase of the study will consist of two overnight stays in a sleep lab in each of two treatment periods, with a minimum one week wash-out in between. After each treatment period the subjects will return for a safety follow-up visit.
Population	The study population will be comprised of patients with SWD. Specifically, these will be night shift workers. A total of approximately 46 men and women aged 18 to 65 years will be enrolled in the study and randomized.

Key Inclusion criteria	• Male and female subjects18 to 65 years of age included. • Confirmed diagnosis of SWD according to ICSD-3 criteria at Screening. • Subjects who are at least moderately ill with respect to sleepiness on work nights, including commute to and from work, as assessed by the Clinical Global Impression-Severity scale (CGI-S, score ≥4) at Screening. • Subjects must work 5 or more night shifts per month, and 2 or more shifts must occur on consecutive nights, with 6 or more hours worked between 10 pm and 8 am, as confirmed by subject at Screening. • Subjects must have mean sleep latency ≤8 minutes on nighttime MSLT at Screening. • Subjects must weigh at least 50 kg at Screening to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m2. BMI = Body weight (kg) / [Height (m)]2
Key Exclusion criteria	• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are willing to use highly effective contraception and an additional barrier method for the required period. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 3 days after stopping investigational drug. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner. • Subjects, for whom it is not safe to discontinue or who are unwilling to discontinue use of modafinil, hypnotics, and antihistamines for the periods specified in the prohibited medication section. • Heavy caffeine consumers, i.e. subjects who consume greater than 850 mg of caffeine per day (approximate equivalent of three tall cups of Starbucks coffee) in coffee, tea, or other caffeine-containing drinks. • Subjects who have high risk of obstructive sleep apnea, indicated by score of 5 or more on the STOP-BANG questionnaire. • Presence of any sleep disorder other than SWD, as confirmed by PSG at screening.
Study treatment	• LML134 • Placebo
Pharmacokinetic assessments	• Population PK model
Efficacy/PD assessments	• MSLT
Key safety assessments	• Adverse event monitoring • Physical examinations • Monitoring of laboratory markers in blood and urine • ECG • Polysomnography
Other assessments	Corporate Confidential Information

Data analysis	Mean sleep latency score data will be analyzed using a mixed effect ANOVA model with treatment and period as fixed effects and subject as a random effect. Least square estimates for each treatment and treatment difference (LML134 vs placebo) along with 95% confidence interval will be reported.
Key words	Shift work disorder, multiple sleep latency test, sleep, polysomnography

1 Introduction

1.1 Background

Shift work disorder (SWD) is a common yet under-recognized and undertreated circadian rhythm sleep disorder. It is caused by a misalignment between the patient's endogenous circadian rhythm and the sleep-wake pattern dictated by the environment. The two prevailing symptoms of SWD are insomnia and excessive sleepiness (ES). The symptoms are associated with shift work that happens, at least in part, during the usual hours of the main sleep episode. SWD occurs despite the patients' attempts to optimize environmental conditions for sleep. The condition usually persists only for the duration of the shift work schedule, but in some individuals, the sleep disturbance may persist beyond the duration of shift work (AASM 2014). SWD has been estimated to affect 10-23% of the approximately 22 million shift workers in the US, which translates into a 2-5% prevalence in the general population (Schwartz and Roth 2006). Patients with SWD report greater mood problems, such as impatience, avoidance of interaction with coworkers, a higher risk of depression, impaired social functioning, and lower coping skills. Patients with SWD also have a higher risk of subjective health complaints, ulcers, and substance abuse. Importantly, the ES and fatigue experienced by SWD patients often causes performance impairment and diminished attentiveness leading to higher risk of accidents both during work and during commute between work and home (Ohayon et al 2002; Folkard and Tucker 2003; Barger et al 2005).

Modafinil is approved in the US for the treatment of ES in SWD, but its efficacy is perceived as modest (Czeisler et al 2005). Moreover, modafinil is associated with increased risk of skin and other hypersensitivity reactions, cardiovascular and neuropsychiatric disorders, which led to the withdrawal of the European marketing authorizations in all indications except for narcolepsy due to an unfavourable benefit-risk assessment EMA (2010).

The histaminergic system is one of the key wake-promoting systems in the brain. Histaminergic neurons are located in the tuberomammillary nucleus (TMN) and fire actively during wakefulness, less frequently during sleep and completely cease firing during rapid eye movement (REM) sleep (Lin et al 2011). Firing rate of histaminergic neurons and histamine (HA) release are regulated by presynaptic H3 receptors (H3R). H3R are Gi/Go-protein coupled receptors with high constitutive activity that inhibit TMN neuron firing and HA release under basal conditions and through activation by HA (Benarroch 2010). Inverse agonists can decrease the constitutive activity of H3R and thereby increase the release of HA in brain leading to increased wakefulness.

Recently, H3R inverse agonists have been evaluated as a potential treatment for ES and cognitive impairment. The first drug, pitolisant (Wakix™) has been approved by the European Medicines Agency (EMA) for the treatment of narcolepsy in 2016. However, the clinical utility of H3R inverse agonists is limited by their major side effect, insomnia, arising from prolonged duration of action. This major side effect might restrict the dose tolerated by patients, and thereby lead to limited efficacy.

The most relevant data for the present study are summarized in the sections below. For detailed information, please refer to the Investigator's Brochure.

1.4 Study purpose

The main purpose of this study is to demonstrate that LML134 can increase wakefulness compared to placebo in patients with SWD measured by objective and subjective endpoints of wakefulness, i.e. the sleep latency in the multiple sleep latency test (MSLT)
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Safety, tolerability and PK of LML134 will also be evaluated in SWD patients. The study is expected to provide information on whether the overall clinical profile of the drug warrants further clinical development in this indication.
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2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	***Endpoints related to primary objective(s)***
• To demonstrate that wakefulness in SWD patients is significantly increased after treatment with LML134 compared to placebo	• Average sleep latency over two consecutive test nights as measured by the MSLT

2.2 Secondary objective(s)

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the safety and tolerability of LML134 compared to placebo in SWD patients	• Standard safety assessments such as vital signs, ECG, hematology, blood chemistry, urinalysis, AE reporting, and daytime PSG to assess drug effect on sleep
• To assess the plasma pharmacokinetics of LML134 in SWD patients	• Due to sparse sampling, only plasma concentrations will be listed and no PK parameter will be evaluated by noncompartmental analysis. The data will be part of the overall Population PK model
• To evaluate the time course of LML134 effect on wakefulness compared to placebo	• MSLT at each time point averaged over two consecutive test nights

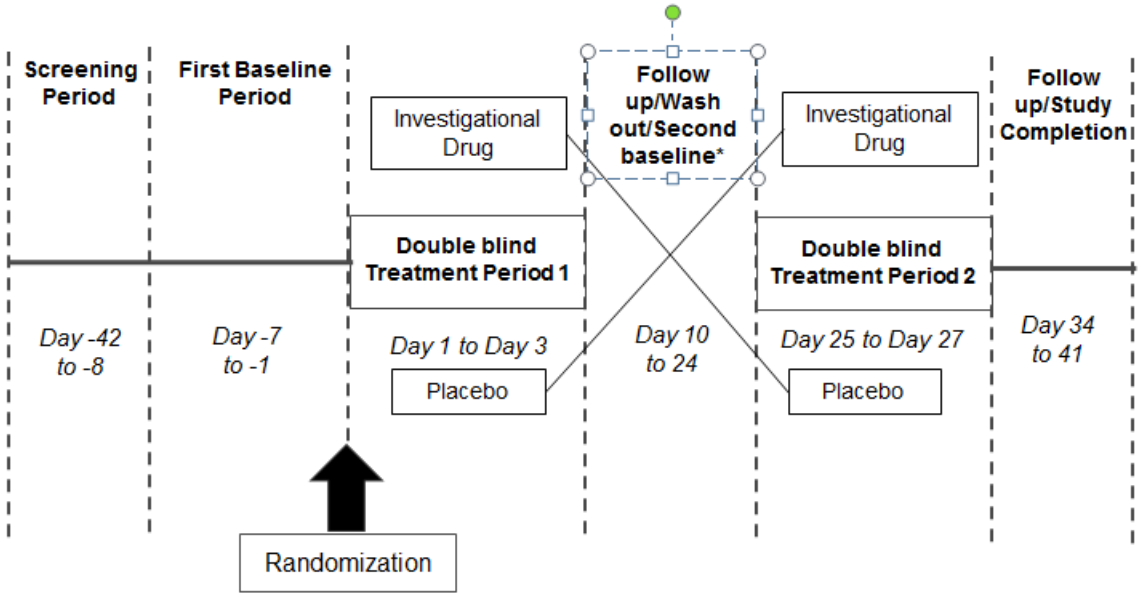
3 Investigational plan

3.1 Study design

This is a randomized, subject and investigator-blinded, placebo controlled, crossover, multi-center Proof of Concept (PoC) study with in-house simulated laboratory night shifts in patients with SWD. This non-confirmatory study will include two treatment arms: LML134 and placebo.

The study will utilize a 2x2 crossover design, with two treatment periods and two sequences as shown in Figure 3-1. Approximately 46 subjects will be randomized in this study. All subjects will receive both treatments (LML134 and placebo), one in each treatment period, with the order of treatment being randomized.

Figure 3-1 Study design



*Second Baseline can be delayed to accommodate a washout period of up to 5 weeks between the last dose in Treatment period 1 and the first dose in Treatment period 2.

An initial screening period will include screening for eligibility including a clinical interview and collection of at least two weeks (14 days) of outpatient paper sleep diary to confirm SWD diagnosis according to ICSD-3 criteria. Subsequently, daytime sleep PSG and nighttime MSLT will be performed in the sleep lab on consecutive days that follow at least 3 consecutive nights awake by the subject to exclude any other sleep disorder and estimate the severity of objective sleepiness, respectively. Timing of screening MSLT naps will correspond to the timing of efficacy MSLT (see assessment table for timing of highly repetitive assessments).

A baseline prior to each treatment period will include an outpatient day visit to perform a variety of baseline assessments as specified in the assessment schedule. The baseline periods will be timed such that the patient completes at least 3 consecutive nights awake (corresponding to their regular shift work schedule) directly prior to coming in to begin the treatment period. The patients will also need to fill out the paper sleep diary during the 3 days before the treatment period. The outpatient baseline visit can take place on any day from day -7 to day -1, however results of the baseline assessments (including safety labs and drug screen) must be available before dosing.

If a patient needs to repeat baseline assessments then a repeat baseline visit can be performed following approval by the sponsor as long as the visit can be performed within the screening window (for baseline 1) or wash-out window (for baseline 2).

During screening and baseline (1 or 2) the required three consecutive nights awake can either include three consecutive working nights shifts in the patients regular work environment or two consecutive working nights shifts in the patients regular work environment and one additional night awake domiciled in the sleep lab. This additional night spent in the sleep lab may occur immediately prior to or after the patients scheduled work shifts and must follow the same schedule as a usual working night shift. Documentation of any additional nights spend in the sleep lab must be documented in the sites source records. The patients will be supervised during the additional night at the sleep lab to avoid napping. Patients may choose to take their daytime sleep at the laboratory following the additional night spent there or may leave the center in the morning. In the latter case, they will be provided with safe transport home. If scheduling permits the patients can remain at the site to begin the treatment period Day 1.

Each treatment period will be comprised of two nights of treatment and concomitant assessments and one day of recovery sleep in between (Day 2). Staying at the study center for recovery sleep on Day 3 is optional. Assessments will be identical in both treatment periods.

After at least three consecutive nights awake following a night shift work schedule (during the baseline period), subjects will begin their daytime period of sleep (Day 1) starting at approximately 10:00 at the sleep laboratory clinical site. Total time spent in bed on Day 1 should be approximately 8 hours. No sleep assessments are performed on Day 1, but other baseline assessments are performed as specified in the Assessment schedule.

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On Night 1, safety assessments, will be performed after daytime sleep but before dosing. If timing of the daytime sleep period would not allow completion of all necessary assessments before dosing, the physical and neurological exams, CSSR-S and alcohol/drug/cotinine screen can be completed before the subject goes to sleep in the morning. The subjects will receive the first dose of assigned drug at approximately 22:00, and will then perform a series of assessments repeated at regular intervals throughout the night. Wakefulness will be assessed using the MSLT at approximately 1:30, 3:30, 5:30 and 7:30.

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Subjects are not allowed to nap during the assessment nights outside the MSLT exams. They will be continuously supervised by site personnel to make sure they stay awake during the test nights.

Subjects will remain in the clinic for recovery sleep during Day 2 starting in the morning at approximately 10:00, and will undergo PSG to assess daytime sleep. Total time spent in bed on Day 2 should be approximately 8 hours.

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Subjects will also be requested to fill out a sleep diary upon waking on the days specified in the Assessment schedule.

Safety assessments, Corporate Confidential Information will be performed again after daytime sleep but before dosing on Day 2, similarly to Day 1. Subjects will receive the second dose of assigned drug at approximately 22:00 on Night 2. Night 2 assessments will be identical to those completed on Night 1 at approximately the same clock time.

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Once all assessments on the morning of Day 3 have been completed, subjects can either remain in the clinic for Day 3 recovery sleep, or will be provided with safe transportation home for recovery sleep, if all safety assessments have been completed with satisfactory results.

Subjects will return to the clinical site for a follow-up visit for safety purposes 7 to 14 days after completion of treatment in both periods. The safety follow-up visit after the first period can also serve as baseline visit for the second period, if Treatment period 2 Day 1 occurs within 7 days of the visit. Sparse PK sampling will be done over the two day study period as indicated in the Assessment schedule to obtain an optimal exposure estimation with the help of the established Pop-PK model.

Treatment periods will be separated by a wash-out of period of up to 5 weeks, depending on each subject's night shift work schedule. This washout should be measured from the last dose in treatment period 1 and the first dose in Treatment period 2. After both treatment periods have been completed and the follow-up safety visits have been completed subjects will undergo End Of Study evaluations and will be discharged from the study.

If subjects discontinue early they should complete the EOS assessments before leaving the sleep lab and return within 7 to 14 days to complete the safety follow-up visit. (unless the subject withdraws the informed consent, see Section 7.3 for details).

3.2 Rationale of study design

Overall study design:

A cross-over study is planned to minimize the number of subjects and control for intra-subject variability during treatment comparison. The use of a subject and investigator-blinded placebo arm is to provide a comparison group for an unbiased collection of efficacy, safety, and tolerability data.

The purpose of the relatively long screening period is to allow time to establish the diagnosis of SWD according to ICSD-3 criteria, which requires assessment of the subject's circadian rhythm over a period of at least two weeks to demonstrate a disturbed sleep and wake pattern determined by a clinical interview and sleep diary data.

During the baseline period, each subject's circadian rhythm needs to be evaluated again with sleep diary data (which provides parameters such as total sleep time, time of going to bed and time of getting out of bed). This is necessary to inform about the subject’s sleep-wake cycles for both treatment periods, as MSLT results can be substantially influenced by duration and quality of sleep before the assessment.

Subjects are required to stay at the sleep center for the entire treatment period, as the primary readout (MSLT) can only be performed at specialized centers.

Choice and timing of efficacy assessments:

The MSLT, which is considered the gold-standard objective measure of sleepiness, was selected as the primary readout to demonstrate the wakefulness promoting effect of LML134. It has successfully been used in previous studies in SWD patients to demonstrate drug effect on sleepiness.

Congruous to the timing of excessive sleepiness in SWD patients, all efficacy assessments will be performed during the night.

Wakefulness will be assessed at regular intervals during the treatment nights, as recommended by relevant guidelines (Littner et al 2005) and also performed in other studies in SWD patients (Czeisler et al 2005; Czeisler et al 2009). MSLT will be timed such that they cover most of the regular interval corresponding to night shifts and the commute home (22:00 to 8:00), as this is the period when SWD patients could benefit from the effect of a wakefulness promoting drug. However, and MSLT will not be performed during the earliest hours of the shift, as no substantial impairment is expected then.

Safety assessments:

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Therefore safety assessments in the present study will be limited to routine monitoring of vitals, ECG, selected lab parameters, brief neurological examination, and AE collection.

LML134 effect on sleep will also be evaluated using PSG as part of the safety assessments. LML134 is expected to promote wakefulness during the night shift without having a clinically significant effect on daytime sleep in SWD patients. PSG is considered the gold standard method to assess sleep.

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Selection of patient population:

Moderately or severely ill patients with ES during the night shift will be enrolled into the study, based on their CGI-S score on sleepiness and MSLT sleep latency. These are the patients who might benefit most from any wakefulness promoting drug. Previous studies with modafinil also recruited patients with similar characteristics.

Sparse PK sampling:

Sparse PK sampling will be done as indicated in the Assessment schedule to obtain an optimal exposure estimation with the help of the established Pop-PK (Population Pharmacokinetics) model. PK (LML134) and PD (sleep duration overnight) data from a Phase I Clinical Study were used for model development. Based on the developed PK model, the optimal experimental design theory was implemented to select the sampling times that would yield the maximum information (Aarons and Ogungbenro 2010). Based on the available resources, the study design is required to meet the following criteria:

- Number of PK samplings should be limited to 7
- Sampling time window should be limited to 36 hours
- Number of subjects should be 46 (2x2 cross-over design)
- Dose amount should be assumed equal

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The calculated optimal sampling times are: predose, 0.25, 2, 3, 12, 24, and 34.5 hours post first dose in each period. By using these sampling times, the PoC study results will allow for accurately (standard error < 50%) estimating all the PK model parameters (but $V_{peripheral}$) for the subjects. Only a longer time window, and not additional sampling time points, could decrease the high uncertainty in estimating $V_{peripheral}$. Given that a longer time window is not feasible, due to the inconvenience that would cause to the subjects, the aforementioned sampling times were finally selected for this study design.

3.3 Rationale for dose/regimen, route of administration and duration of treatment

Treatment duration

In each treatment period, subjects will receive the study drug on two consecutive nights. H3R inverse agonists, like LML134, rapidly increase histamine release in the brain after administration. Corporate Confidential Information

It is therefore expected that a single dose of LML134 will have wakefulness promoting effects and a single administration of the drug would be enough to assess its efficacy. Clinical studies with other H3R inverse agonists have verified that a single dose of the compound can indeed promote wakefulness and prolong sleep latency (Iannone et al 2010).

The variability of MSLT sleep latency is large, particularly in multi-center studies. Therefore two nights of treatment are planned in the present study to allow calculation of mean sleep latency over the two-night period. The averaged readouts are expected to provide more robust results with lower variability than the single night readouts.

Treatment periods will be separated by a wash-out of 1-5 weeks, depending on each subject's night shift work schedule. Additionally, this washout period covers at least 5-times the half-life of LML134 (4.6 hours to 7.6 hours) to allow complete washout of LML134 from the body.

Dose of LML134 and time of administration

The dose of LML134 used in the present study is guided by results of the occupancy PET study and the PK/PD model based on the FIH study.

It is known from the literature (Iannone et al 2010) Corporate Confidential Information that at least 80% of RO is needed to reach full efficacy of H3R inverse agonists. SWD patients could benefit from the wakefulness promoting effect of LML134 during the hours that correspond to the night shift (from 22:00 to 6:00) and during the additional hours that cover the usual time of commute to home (from 6:00 to 8:00). It is, however, also important to minimize the impact of LML134 on daytime sleep (starting at about 10:00) following the simulated night shift. Therefore the selected dose of LML134 is expected to provide full wakefulness promoting effect for the entire duration of the simulated shift but also minimize effect on daytime sleep duration.

The main principle that guides selection of the LML134 dose is that RO should be sufficiently high to provide full efficacy during the entire simulated night shift. Therefore the dose of LML134 will be such that it is expected to provide >80% RO and thus full efficacy for about 10 hours post dose in 90% of the subjects. Corporate Confidential Information

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Thus study drug will be administered at approximately 22:00, at the beginning of the simulated night shift.

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LML134 has a short half-life (4.6 hours to 7.6 hours). Corporate Confidential Information

Thus accumulation of LML134 exposure is not expected to lead to a further reduction in total sleep time compared to the first post-dose sleep period.

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3.4 Rationale for choice of comparator

The use of a placebo arm will provide a comparison group for an unbiased collection of efficacy, safety, and tolerability data. In most countries there is no regulatory approved treatment for excessive sleepiness in SWD, therefore placebo is an appropriate comparator.

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3.6 Risks and benefits

There is no benefit expected for subjects participating in this study.

The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, in-patient setting, use of study-stopping rules, short duration of treatment, and assurance of safe transport home.

Following re-evaluation of safety data women of childbearing potential are eligible to participate in the study if they are willing to use highly effective contraception to prevent pregnancy, from start of the first treatment period until 3 days after the completion of the second treatment period and an additional barrier method while taking the study drug and for 3 additional days in both treatment periods. There may be unknown risks of LML134 to an unborn human fetus or a nursing child that are not known and may be serious.

Sexually active males must be informed of the requirement to wear a condom for the following reasons:

- Prevent pregnancy in a female partner

AND

- Prevent delivery of investigational drug via seminal fluid to their partner as study treatment may involve unknown risks to the fetus if pregnancy were to occur

There may be unknown risks of LML134 which may be serious.

3.6.1 Blood sample volumes

A maximum of 500 mL of blood is planned to be collected from each subject as part of the study. The study has a maximum duration of around 18 weeks (including the maximum 5 week washout period between treatment periods) . Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central Laboratory Manual.

4 Population

SWD patients

The study population will be comprised of patients with SWD. Specifically, they will be night shift workers (permanent or rotating).

A total of approximately 46 subjects will be enrolled in the study and randomized. Replacement subjects may be enrolled to replace subjects who discontinue the study for reasons other than safety.

The Investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening and the relevant eligibility criteria at both baselines. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

4.1 Inclusion criteria

SWD patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects 18 to 65 years of age included.
3. Diagnosis of SWD according to ICSD-3 criteria confirmed by a Clinical Interview at Screening supported by sleep diary results recorded for at least 2 weeks. Sleep diary results must be available at a minimum 4 days per week (during the 2 weeks of recording).
4. Subjects who are at least moderately ill with respect to sleepiness on work nights, including commute to and from work, as assessed by the Clinical Global Impression-Severity scale (CGI-S, score ≥4) at Screening.
5. Subjects must work 5 or more night shifts per month, and 2 or more shifts must occur on consecutive nights, with 6 or more hours worked between 10 pm and 8 am (22:00 and 8:00), as confirmed by subject at Screening.

6. Subjects must have mean sleep latency ≤8 minutes on nighttime MSLT at Screening.
7. Subjects must weigh at least 50 kg at Screening to participate in the study, and must have a body mass index (BMI) within the range of 18 - 35 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2
8. At screening and each baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed in the sitting position. Sitting vital signs should be within the following ranges:
   - oral body temperature between 35.0-38.0 °C
   - systolic blood pressure, 90-159 mmHg
   - diastolic blood pressure, 50-99 mmHg
   - pulse rate, 40-100 bpm

   If vital signs are outside these ranges, the Investigator may obtain two additional readings, so that up to three consecutive assessments are made, following the procedure in the SOM. At least the last readings must be within the ranges provided above in order for the subject to qualify.
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

SWD patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or within 30 days, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
3. History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects participating in the study such as:
   - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   - History of familial long QT syndrome or known family history of Torsades de Pointes
4. Current use of a pacemaker.
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
6. Score “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, at Screening or each Baseline, if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal Self-Injurious Behavior” (item also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years.
7. Pregnant or nursing (lactating) women.

8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception from start of taking the study medication in the first period until stopping the medication in the second treatment period and for 3 additional days after AND an additional barrier method of contraception will be used while taking the study medication and for 3 additional days in both treatment periods.

   Highly effective contraception methods include:

   - Female sterilization (have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
   - Male sterilization (at least 6 m prior to screening). The vasectomized male partner should be the sole partner for that subject
   - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

   In case of use of oral hormonal contraception or other forms of hormonal contraception (e.g. vaginal ring or transdermal patch) women should have been stabile on the same pill/method for a minimum of 3 months before starting study treatment. In case of use of an IUD or IUS, the device or system should have been placed and well tolerated by the patient for a minimum of 3 months before starting the study treatment.

   Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential
9. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 3 days after stopping investigational drug in both study periods. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner.
10. Heavy smokers who smoke more than 10 cigarettes a day and occasional or light smokers (not more than 10 cigarettes per day) who are not willing to, or in their own or the investigators opinion are not able to refrain from tobacco/nicotine use for at least 12 hours without nicotine craving or other withdrawal symptoms (e.g. anxiety, irritability, restlessness, sweating, headache, etc.).

11. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The Investigator should make this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
    - History (past 5 years) of inflammatory bowel disease, peptic ulcers, gastrointestinal including rectal bleeding with the exception of bleeding from otherwise asymptomatic hemorrhoids;
    - Any history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
    - History (past 5 years) of pancreatic injury or pancreatitis;
    - Liver disease or liver injury as indicated by abnormal liver function tests as specified below. ALT (SGPT), AST (SGOT), γ-GT, alkaline phosphatase, and serum bilirubin will be tested.
        - Serum bilirubin must not exceed 1.2 x ULN
        - γ-GT, ALT, AST, and alkaline phosphatase must not exceed 1.5 x ULN
    - History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g. albuminuria).
    - Evidence of urinary obstruction or difficulty in voiding at Screening.
12. History of hematological diseases in the past 5 years.
13. Abnormalities on hematology lab tests at Screening or either Baselines that are considered clinically relevant by the Investigator.
14. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
15. Chronic infection with Hepatitis B (HBV) or Hepatitis C (HCV). A positive HBV surface antigen (HBsAg) test, or if standard local practice, a positive HBV core antigen test, excludes a subject. Subjects with a positive HCV antibody test should have HCV RNA levels measured. Subjects with positive (detectable) HCV RNA should be excluded.
16. Any clinically significant infectious disease which has not resolved within 2 weeks prior to dosing.
17. Vaccination with any live, attenuated vaccine in the 3 months prior to dosing.
18. History of unstable thyroid disease in the past 5 years or any clinically relevant abnormality on plasma thyroid stimulating hormone test (TSH) at Screening. Thyroid disease that is stable and well-controlled with hormone supplementation but without antithyroid medication is acceptable if TSH is normal at Screening and hormone supplementation dose has been stable for at least 12 months prior to Screening.
19. History of drug abuse or unhealthy alcohol use[#] within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays conducted during Screening or each Baseline.
    [#]Unhealthy alcohol use is defined as a history of, or current alcohol misuse/abuse, defined as "Five or more drinks on the same occasion on each of 5 or more days in the past 30 days."

20. History of recreational cannabis use within four weeks prior to dosing, or evidence of such use as indicated by the laboratory assays conducted during Screening or each Baseline. This exclusion criterion applies even if cannabis use is legalized where the site is located. Any prescribed, medicinal use of cannabis is to be handled according to the prescription drug usage criteria defined below.
21. Use of any medication specified in the prohibited medication section.
22. Subjects, for whom it is not safe to discontinue or who are unwilling to discontinue use of modafinil, hypnotics, and antihistamines for the periods specified in the prohibited medication section.
23. Heavy caffeine consumers, i.e. subjects who consume greater than 850 mg of caffeine per day (approximate equivalent of three tall cups of Starbucks coffee) in coffee, tea, or other caffeine-containing drinks.
24. History of any neurological or psychiatric disorders in the past 5 years, with the exception of a short duration depressive episode, if it has completely resolved at least 12 months before Screening.
25. History of epilepsy or of seizures or convulsions of any kind in the past 5 years.
26. History of head trauma leading to clinically significant symptoms in the past 5 years.
27. Any history of any chronic eye disease affecting the retina.
28. Any history of surgery on the retina, including laser treatment, or plans for such surgery during the study.
29. Subjects who have high risk of obstructive sleep apnea, indicated by score of 5 or more on the STOP-BANG questionnaire.
30. Presence of any sleep disorder other than SWD, as confirmed by PSG at Screening. Specifically, the subjects must present with apnea-hypopnea index (AHI) <15 and periodic leg movement in sleep with arousal index (PLMSArI) < 15.
31. Any general medical condition that could account for excessive sleepiness during night shifts.
32. Considered by the investigator to be unlikely to comply with the study protocol
33. At screening or each baseline, presence of any such medical condition or abnormalities on safety examinations that are not mentioned among the exclusion criteria above, but indicate significant risk of safety for subjects participating in the study.

Repeat Laboratory assessments: In the case where a safety laboratory assessment at Screening or either Baseline is outside of the range specified above, the assessment may be repeated once prior to randomization/treatment. If the repeat value remains outside of the specified ranges, the subject is excluded from the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of child bearing potential must be willing to use a highly effective contraception from start of taking the study treatment in the first treatment period to completing the study treatment in the second treatment period and for 3 additional days after AND also willing to use an additional barrier method of contraception while taking the study medication and for 3 additional days after in both treatment periods. Highly effective contraception methods are one of the following:

- Female sterilization (have had surgical bilateral ophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
- Male sterilization (at least 6 m prior to screening). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral hormonal contraception or other forms of hormonal contraception (e.g. vaginal ring or transdermal patch) women should have been stabile on the same pill/method for a minimum of 3 months before starting study treatment. In case of use of an IUD or IUS, the device or system should have been placed and well tolerated by the patient for a minimum of 3 months before starting the study treatment.

Barrier contraception methods include: male condom, female condom, diaphragm or cervical cap. Spermicide must be used with diaphragm and cervical cap.

Women of child bearing potential are defined as all women physiologically capable of becoming pregnant. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

Sexually active males should be reminded of the requirement to wear a condom for 3 days after the last administration of investigational drug for the following reasons:

- Prevent pregnancy in a female partner

AND

- Prevent delivery of investigational drug via seminal fluid to their partner as study treatment may involve unknown risks to the fetus if pregnancy were to occur

If there is any question that the subject will not reliably comply, the subject should not be entered or continue in the study. Male subjects should be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information. Please refer to Section 4.2 (Exclusion criteria) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after the indicated period.

Table 5-1 Prohibited medication

Medication	Prohibited period	Action to be taken
Drugs that are known to strongly inhibit or induce the metabolizing enzymes CYP3A4/5, as they may alter the PK of LML134.	From at least 5 half-lives before first dosing through end of study	Do not enroll subject or initiate treatment. Discontinue study treatment during treatment periods.
Drugs or other non-pharmacological interventions that might affect circadian rhythm (e.g. melatonin, light therapy).	From start of screening through end of study.	Do not enroll subject or initiate treatment. Discontinue study treatment during treatment periods.
Modafinil and hypnotics	From at least 5-times the half-life of the drug prior to the start of screening through end of study.	Do not enroll subject or initiate treatment, unless it is safe to discontinue modafinil and hypnotics and the subject agrees to discontinue use of modafinil and hypnotics. Should the need arise for a subject to take modafinil or hypnotics during the study, the study drug should be discontinued.
All CNS-active medication including OTC cough suppressant (except modafinil and hypnotics)	From start of screening through end of study.	Do not enroll subject or initiate treatment. Should the need arise for a subject to take CNS active medication during the study, the study drug should be discontinued.
Antihistamines, in particular, first generation (i.e. brain penetrant, sedative) antihistamines (chlorpheniramine, diphenhydramine, promethazine, and hydroxyzine)	From at least 5-times the half-life of the drug prior to the start of screening through end of study.	Do not enroll subject or initiate treatment, unless it is safe to discontinue antihistamines and the subject agrees to discontinue use of antihistamines. Should the need arise for a subject to take antihistamines during the study, the study drug should be discontinued.

Medication	Prohibited period	Action to be taken
Any other drug, herbal or food supplement that might induce sleepiness/somnolence or sedation as a known and common AE (>1%) according to the label of the drug and medical history of the subject indicates that the excessive sleepiness might be related to use of these drugs or food supplements. Examples include antiemetics, alpha-adrenergic blocking agents, some beta adrenergic blocking agents, muscle relaxants and other drugs.	From start of screening through end of study.	Do not enroll subject or initiate treatment. Should the need arise for a subject to take such medication during the study, the study drug should be discontinued.
Combination drug treatments that contain caffeine.	From at least 12 hours before dosing to end of assessments during the treatment period	Discontinue study treatment and remove subject from efficacy analysis.

5.3 Dietary restrictions and smoking

- No alcohol for 12 hours before each dosing. Consumption of alcohol is not permitted at any time while the subjects are domiciled. During the out-patient phase of the study consumption of alcohol will be restricted to no more than one drink per day for women and no more than two drinks per day for men. A standard drink (in the United States) is equal to 14.0 grams (0.6 ounces) of pure alcohol. Generally, this amount of pure alcohol is found in
  - 12 fluid ounces of regular beer (5% alcohol content)
  - 5 fluid ounces of wine (12% alcohol content)
  - 1.5 fluid ounces or a “shot” of 80-proof (40% alcohol content) distilled spirits or liquor (e.g., gin, rum, vodka, whiskey)
- No cannabis use for 4 weeks before first dosing until after Study Completion evaluation.
- Smokers should not smoke more than 10 cigarettes per day during the entire study period. Consumption of nicotine containing products is also restricted to equivalent amount (corresponding to 10 cigarettes) during the entire study period. Smoking is completely prohibited during the treatment period each night from about 2 hours before dosing until completion of all efficacy assessments.
- Intake of methlyxanthine (e.g. caffeine, theophylline, theobromine) containing food or beverages must be discontinued 12 hours before dosing. Consumption of such foods and beverages (i.e., coffee, tea, soda, chocolate) is not permitted at any time while the subjects are domiciled. During the out-patient phase of the study caffeine consumption will be restricted to no more than 850 mg of caffeine per day.
- No grapefruit or grapefruit juice is to be consumed for 14 days prior to dosing until 7 days following the last dose.

Subjects should take medication when administered by site staff. Study medication should be administered with a glass of water. Subjects should not chew the medication, but swallow it whole.

Meals and snacks will be served at appropriate times according to the subjects' sleep/wake schedules and so as not to interfere with the Assessment schedule. Subjects will follow a standard weight maintaining diet while domiciled.

5.4 Other restrictions

Not applicable.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Site Operations Manual.

6.1.1 Investigational treatment and control drug(s)

Table 6-1 Overview of study medication

Study drug name	Formulation	Appearance	Unit dose	Packaging	Provided by
LML134	Capsule	Corporate Confidential Information		Open label bulk	Novartis
Placebo	Capsule	Corporate Confidential Information		Open label bulk	Novartis

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Study treatments are defined as:

- A: single dose of LML134, on each of two consecutive nights
- B: single dose of placebo to LML134, on each of two consecutive nights

Subjects will be randomized to one of the following 2 treatment sequences in the ratio of 1:1.

Table 6-2 Definition of treatment sequences

Sequence	Period 1	Period 2
1	A	B
2	B	A

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number, which will be in the range of 5101-5146.

The randomization number is only used to identify which treatment the subjects have been randomized to receive. The Subject number assigned to a subject at Screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

Replacement randomization numbers will be in the range of 6101-6146. If a subject requires a replacement, the replacement subject will be assigned a randomization number corresponding to the original subject (e.g. Subject 6103 would replace Subject 5103). Any additional subjects enrolled will use sequential subject numbering.

Table 6-3 details the general details of the numbering of the subjects once randomized to treatment.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Subjects will be randomized within the electronic NIRT system. Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

Table 6-3 Treatment Assignment Numbering

Cohort	Randomization numbers	Replacement randomization numbers
I (n = 46)	5101 - 5146	6101 - 6146

6.4 Treatment blinding

This is a subject- and investigator-blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of any unblinded site staff identified below, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Drug product will be supplied in bulk, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive a randomization list or treatment allocation cards from Drug Supply Management with the appropriate treatment allocation numbers. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study:

- Unblinded field monitor(s)
- Unblinded sample analyst(s) (PK)

The unblinded field monitors are required to review drug accountability and allocation at site. The unblinded monitors are not provided with a randomization list directly but will be unblinded through review of source documentation compiled by the unblinded pharmacist, which details treatment allocation to individual subjects. The unblinded monitors will also be able to review the treatment allocation cards/randomization list provided to the unblinded pharmacist. The names of the unblinded monitor(s) are detailed in the Monitoring Plan.

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-4. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g. biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The clinical trial team is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-4 Blinding and unblinding plan

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	B	UI	UI	UI
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	B	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
Independent committees used for assessing interim results	NA	NA	NA	NA
All other sponsor staff not identified above	B	B	UI	UG

B Remains blinded

NA Not applicable

UI Allowed to be unblinded on individual patient level

UG Allowed to be unblinded on treatment group level

6.5 Treating the subject

LML134 will be administered to the subject orally at the study site once a day in the evening.

LML134 and Placebo will be provided as capsules. Corporate Confidential Information

See the Site Operations Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments and/or interruptions are not permitted.

6.7 Emergency breaking of assigned treatment code

Emergency unblinding must only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition.

Emergency treatment code breaks are performed using the NIRT system. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The investigator must also immediately inform the study monitor that the code has been broken.

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LML134, as detailed in Section 8.7.

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

6.9 Recommended treatment of adverse events

There is no specific antidote to LML134. Any adverse events should be managed symptomatically according to standard of care and applicable clinical guidelines.

In case of insomnia, non-pharmacological treatments should be attempted first.

6.10 Rescue medication

Not applicable.

6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes or any change in dose of known medication after the subject was enrolled into the study and until the study completion.

All medications, vaccinations, over-the-counter drugs and significant non-drug therapies (including physical therapy, light therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria and prohibited medication sections until Study Completion, must be reported in the CRF on the Concomitant medications/Significant non-drug therapies page after the start of the study.

Medication entries should be specific to trade name, the route of administration, the start and discontinuation date, and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

Study completion is defined as when the last subject completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration. Discontinuation of study treatment can be decided by either the subject or the investigator.

Study treatment must be discontinued under the following circumstances:

- Subject decision - subjects may choose to discontinue study treatment for any reason at any time.
- The investigator believes that continuation would negatively impact the safety of the subject or the risk/benefit ratio of trial participation.
- Any protocol deviation that results in a significant risk to the subject's safety or loss of significant data.
- Any occurrence of protocol exclusion criteria #6, #13, #19, #20, at the second Baseline visit.
- Pregnancy (see Section 8.6 (Safety) and Section 9.6 (Pregnancy reporting))
- Use of prohibited treatment as described in the relevant section
- Emergence of the following adverse events:
    - An SAE (including seizure) that is suspected to be related to study drug
    - An AE which is severe and suspected to be related to study drug
    - Infection of clinical concern, independent of the nature of the infection
    - Hyperthyroidism, evidenced by symptoms consistent with the clinical manifestation of the disease and confirmed by lab results of thyroid hormone levels

  - Any impairment or blurring of vision or other visual complaints that might suggest retinal damage (e.g. curtain like shadow in the visual field, seeing sparks or flashes of light, appearance of many floaters, etc)
  - Any significant change in behavior of the subject (e.g. signs of confusion, agitation or other symptoms indicating emerging psychiatric problems)
- Liver events, as defined in Table 15-2-Appendix 1 of the protocol
- Renal events, as defined in Table 16-1 Appendix 2 of the protocol
- Any of the following laboratory abnormalities:
  - Total white blood cell count <2000 cells/mm; <2.0 x 10e9 /L
  - Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L
  - Any other laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- The following deviations from the prescribed dose regimen for the study drug
  - One or more missed doses
  - Dose of study drug was different from that specified in the study protocol

The appropriate personnel from the site and Novartis will assess whether investigational drug treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

If discontinuation of study treatment occurs, investigator must determine the primary reason for the subject's premature discontinuation of study treatment.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 7.3, Withdrawal of informed consent). Where possible EOS assessments should be completed before they leave the sleep laboratory and they should be requested to return within 7 to 14 days to complete the follow-up visit. If they fail to return for future visits for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 7.4. (Lost to follow-up). This contact should preferably be done according to the study visit schedule,

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new / concomitant treatments
- adverse events/Serious Adverse Events

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable attempt (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

The study will be stopped, and no further dosing decisions will be taken pending a full safety review, if any of the following criteria are met:

- 1 or more study-drug related SAEs (including seizure) are reported
- 1 or more subjects in the study experience study-drug related newly emerging symptoms indicating retinal damage, if the retinal damage is confirmed by appropriate ocular examinations
- 2 or more subjects in the study experience any of the following:
  - Total white blood cell count below 2000 cells/mm; 2.0 x 10e9/L
  - Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L
- 4 or more subjects in the study experience any of the following:
  - Symptoms of hyperthyroidism with elevated thyroid hormone levels in blood
  - A similar AE which is assessed as either moderate or severe in intensity, and is potentially related to study-drug
- The Principal Investigator (or his/her designee) and the Sponsor consider that the number and/or severity of adverse events justify discontinuation of the study
- General Note: In the case where a safety laboratory assessment are outside of the range specified above, the assessment may be repeated once. If the repeat value remains outside of the specified ranges, the stopping rule is met.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the Assessment Schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule

Epoch	Screening		Treatment Period 1														Treatment Period 2			
Visit Name	Screening	Baseline 1	Period 1 Day 1				Period 1 Day 2						Period 1 Day 3		EOS/ET	Follow-up visit 1	Baseline 2	Period 2 Day 1			
Visit Numbers[1]	1[13,14]	101[14,8]	102				103						104		199[15]	1999[16,17]	201[19,8,16]	202[19]			
Days	-42 to -8	-7 to -1	1				2						3		10 to 17	10 to 17	17 to 24	25			
Time (post-dose)	-	-	-2h[20, 21]	0h[22]	0.25h	2h	3h	9.5h[23]	12h[24]	22h	24h[22]	26h	34.5h[15,25]		-	-	-	-2h[20, 21]	0h[22]	0.25h	2h
Subjects domiciled			X															X			
Informed consent	X																				
Corporate Confidential	X																				
Inclusion / Exclusion criteria	X	X															X[26]				
Medical history/current medical conditions	X																				
Demography	X																				

Epoch	Screening		Treatment Period 1														Treatment Period 2			
Visit Name	Screening	Baseline 1	Period 1 Day 1				Period 1 Day 2					Period 1 Day 3		EOS/ET	Follow-up visit 1	Baseline 2	Period 2 Day 1			
Visit Numbers[1]	1[13,14]	101[14,8]	102				103					104		199[15]	1999[16,17]	201[19,8,16]	202[19]			
Days	-42 to -8	-7 to -1	1				2					3		10 to 17	10 to 17	17 to 24	25			
Time (post-dose)	-	-	-2h[20, 21]	0h[22]	0.25h	2h	3h	9.5h[23]	12h[24]	22h	24h[22]	26h	34.5h[15,25]	-	-	-	-2h[20, 21]	0h[22]	0.25h	2h
Physical Examination	X		X										X	X	X		X			
Neurological Examination[2]	X		X										X	X	X		X			
ECG evaluation	X	X	X			X			X	X		X	X	X	X	X	X			X
Sleep diary	X	X[3]	X[4]							X[4]						X[3]	X[4]			
Polysomnography	X								X											
STOP-BANG questionnaire	X																			
Columbia-Suicide Severity Rating Scale	X	X	X										X	X	X	X	X			
Hepatitis and HIV Screen[5]	X																			
Pregnancy and fertility testing	X[6]	X[6]	X[7]										X[6]	X[6]	X[6]	X[6]	X[7]			
Randomization			X																	
Study drug administration				X							X							X		
Body Height	X																			
Body Weight	X	X	X										X	X	X	X	X			
Body Temperature	X	X	X										X	X	X	X	X			
Blood Pressure	X	X	X			X			X	X		X	X	X	X	X	X			X
Pulse rate	X	X	X			X			X	X		X	X	X	X	X	X			X

Epoch	Screening		Treatment Period 1														Treatment Period 2			
Visit Name	Screening	Baseline 1	Period 1 Day 1				Period 1 Day 2						Period 1 Day 3		EOS/ET	Follow-up visit 1	Baseline 2	Period 2 Day 1			
Visit Numbers[1]	1[13,14]	101[14,8]	102				103						104		199[15]	1999[16,17]	201[19,8,16]	202[19]			
Days	-42 to -8	-7 to -1	1				2						3		10 to 17	10 to 17	17 to 24	25			
Time (post-dose)	-	-	-2h[20, 21]	0h[22]	0.25h	2h	3h	9.5h[23]	12h[24]	22h	24h[22]	26h	34.5h[15,25]		-	-	-	-2h[20, 21]	0h[22]	0.25h	2h
Hematology[8]	X	X													X	X	X				
Clinical Chemistry[8]	X	X													X	X	X				
Urinalysis[8]	X	X													X	X	X				
Alcohol Test, Drug Screen, and Cotinine Test[5,8]	X	X	X														X	X			
Corporate Confidential Information	See table below																				
MSLT	See table below																				
Corporate Confidential Information	See table below																				
	X												X								
									X[10]												
				X							X								X		
PK blood collection				X	X	X	X		X		X		X						X	X	X
Corporate Confidential		X																			
Serious Adverse Events	X																				
Adverse Events	X																				
Concomitant therapies		X																			
Study completion															X	X[12]					

Epoch	Screening		Treatment Period 1														Treatment Period 2			
Visit Name	Screening	Baseline 1	Period 1 Day 1				Period 1 Day 2					Period 1 Day 3	EOS/ET	Follow-up visit 1	Baseline 2	Period 2 Day 1			
Visit Numbers[1]	1[13,14]	101[14,8]	102				103					104	199[15]	1999[16,17]	201[19,8,16]	202[19]			
Days	-42 to -8	-7 to -1	1				2					3	10 to 17	10 to 17	17 to 24	25			
Time (post-dose)	-	-	-2h[20, 21]	0h[22]	0.25h	2h	3h	9.5h[23]	12h[24]	22h	24h[22]	26h	34.5h[15,25]	-	-	-	-2h[20, 21]	0h[22]	0.25h	2h
information																				
Corporate Confidential Information													X							
Comments	X																			
Safety Follow up Call																				

Epoch	Treatment Period 2							EOS	Follow-Up visit 2
Visit Name	Period 2 Day 2					Period 2 Day 3		EOS	Follow-Up visit 2
Visit Numbers[1]	203					204		299[15]	2999[17]
Days	26					27		34 to 41	34 to 41
Time (post-dose)	3h	9.5h[23]	12h[24]	22h	24h[22]	26h	34.5h[25]	-	-
Subjects domiciled	X								
Informed consent									
Corporate Confidential									
Inclusion / Exclusion criteria									
Medical history/current medical conditions									
Demography									
Physical Examination							X	X	X
Neurological Examination[2]							X	X	X
ECG evaluation			X	X		X	X	X	X
Sleep diary				X[4]					
Polysomnography			X						
STOP-BANG questionnaire									
Columbia-Suicide Severity Rating Scale							X	X	X
Hepatitis and HIV Screen[5]									
Pregnancy and assessments of fertility							X[6]	X[6]	X[6]
Randomization									
Study drug administration					X				
Body Height									
Body Weight							X	X	X
Body Temperature							X	X	X
Blood Pressure			X	X		X	X	X	X
Pulse rate			X	X		X	X	X	X
Hematology[8]								X	X

Epoch	Treatment Period 2							EOS	Follow-Up visit 2
Visit Name	Period 2 Day 2					Period 2 Day 3		EOS	Follow-Up visit 2
Visit Numbers[1]	203					204		299[15]	2999[17]
Days	26					27		34 to 41	34 to 41
Time (post-dose)	3h	9.5h[23]	12h[24]	22h	24h[22]	26h	34.5h[25]	-	-
Clinical Chemistry[8]								X	X
Urinalysis[8]								X	X
Alcohol Test, Drug Screen, and Cotinine Test[5,8]									
Corporate Confidential Information	See table below								
MSLT	See table below								
Corporate Confidential Information	See table below								
							X		
			X[10]						
		X				X			
PK blood collection	X		X		X		X		
Corporate Confidential									
Serious Adverse Events	X								
Adverse Events	X								
Concomitant therapies	X								
Study completion information							X	X	X
Corporate Confidential Information							X		
Comments	X								X
Safety Follow up Call							X[18]	X[18]	

[X] Assessment to be recorded in the clinical database
[1] Visit structure given for internal programming purpose only
[2] Abbreviated neurological exam only.
[3] Sleep diary should be completed during baseline for 3 days prior to dosing, in conjunction with the patients 3 awake nights even if 1 awake night is spent at the sleep lab
[4] Sleep diary to be completed when subject wakes up from sleep.
[5] Source only.
[6] Serum Pregnancy test. Fertility assessment required at screening only.
[7] Urine pregnancy test acceptable
[8] Results of the baseline assessments (including safety labs and drug screen) must be available before dosing.

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[12] Completion for this Treatment Period.
[13] Screening assessments will occur over multiple days. The daytime sleep PSG and nighttime MSLT will be performed in the sleep lab on consecutive days that follow at least 3 consecutive nights following a shift work schedule.
[14] If a subject spends an additional supervised night in the sleep lab to complete their third consecutive awake night this must be documented in the sites source records. Records should include the date of the stay and the schedule they followed during their stay.
[15] EOS/ET assessments should not be repeated if performed during the follow-up visit at the end of the Treatment Period. If subjects terminate early the EOS assessments should be completed prior to the patient leaving the sleep laboratory and the patient should return for the follow-up visit.
[16] The Follow-up visit in Treatment Period 1 can also serve as the Baseline 2 visit if Treatment Period 2 Day 1 will begin within 7 days after the visit
[17] Follow-up assessments should be completed for any patient who receives test drug 7 to 14 days after they discontinue study treatment in each treatment period.
[18] Safety follow-up phone call to be performed 30 days after last visit for enrolled subjects.
[19] Up to 5 weeks wash out is allowed between the last dose in Treatment period 1 and the first dose of period 2 to allow for scheduling flexibility. Timing of the second baseline visits should be adjusted accordingly.
[20] The assessments should be performed as close as possible to the dosing time. If timing of the daytime sleep period would not allow completion of all necessary assessments before dosing, the physical and neurological exams, CSSR-S and alcohol/drug/cotinine screen can be completed before the subject goes to sleep in the

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[22] Dosing should be performed at approximately 22:00.
[23] 9.5h assessments are detailed in the details for night time assessments table
[24] Safety assessments may commence after completion of efficacy assessments.
[25] Safety assessments should be done prior to discharge. These assessments can be completed after the efficacy assessments Corporate Confidential are completed, if the patients decide to leave the site in the morning. If the subject stays in the clinic to sleep these assessments can be done after the recovery sleep is completed
[26] Any occurrence of protocol exclusion criteria #6, #13, #19, #20, at the second Baseline visit would result in discontinuation

Details for night time (highly repetitive) assessments

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Epoch	Visit Name	Visit Numbers	Days	Time (post-first dose)	Dosing	MSLT
Screening	Screening	1[1]	-42 to -8	-		X
	Baseline 1	101	-7 to -1	-		
Treatment Period 1	Day 1	102	1	-2h		
				0h	X	
	Day 2	103	2	2.5h		
				3.5h		X
				4.5h		
				5.5h		X
				6.5h		
				7.5h		X
				8.5h		
				9.5h		X
				22h		
				24h	X	
	Day 3	104	3	26.5h		
				27.5h		X
				28.5h		
				29.5h		X
				30.5h		
				31.5h		X
				32.5h		
				33.5h		X
	Baseline 2	201	17 to 24	-		

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Epoch	Visit Name	Visit Numbers	Days	Time (post-first dose)	Dosing	MSLT
Treatment Period 2	Day 1	202	25	-2h		
				0h	X	
	Day 2	203	26	2.5h		
				3.5h		X
				4.5h		
				5.5h		X
				6.5h		
				7.5h		X
				8.5h		
				9.5h		X
				22h		
				24h	X	
	Day 3	204	27	26.5h		
				27.5h		X
				28.5h		
				29.5h		X
				30.5h		
				31.5h		X
				32.5h		
				33.5h		X

[X] Assessment to be recorded in the clinical database

[1] Screening assessments will occur over multiple days. The daytime sleep PSG and nighttime MSLT will be performed in the sleep lab on consecutive days that follow at least 3 consecutive night following a shift work schedule.

[2] This time point for practice only. Data will not be collected.

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators a proposed informed consent form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the Site Operations Manual for a complete list of Informed Consent Forms included in this study.

8.3 Subject screening

It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

The initial screening period will include a daytime visit where eligibility will be assessed. This will be followed by at least two weeks (14 days) when the patient continues with their usual work schedule and will fill out a paper sleep diary (outpatient). The patient will come into the sleep lab to complete the inpatient daytime sleep PSG and nighttime MSLT on the day that directly follows at least 3 consecutive nights awake conforming to that subject's night shift schedule.

Information on what data should be collected for screening failures is outlined in the Site Operations Manual.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the Site Operations Manual.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.4.1 Hepatitis and HIV Screen

All subjects will be screened for HIV, Hepatitis B and C. See the Site Operations Manual for details.

8.4.2 Alcohol Test, Drug Screen, and Cotinine Test

All subjects will be screened for substances of abuse and cotinine. See the Site Operations Manual for details, including what information must be captured in the source documentation and CRF for smokers.

8.4.3 STOP-BANG questionnaire

The STOP-BANG questionnaire was designed to screen for symptoms of obstructive sleep apnea (OSA) in surgical patients Chung et al 2008, but was validated in broader population referred to a sleep laboratory for overnight PSG Boynton et al 2013. Subjects will complete the questionnaire during screening to assess eligibility prior to the subject completing the 14 days of sleep diary. See the SOM for details.

8.5 Efficacy / Pharmacodynamics

8.5.1 MSLT

The MSLT is a validated objective measure of the ability or tendency to fall asleep. It is intended to measure physiological sleep tendency in the absence of alerting factors. The MSLT is based on the assumption that physiological sleepiness decreases sleep latency. That is, the tendency to fall asleep should increase as physiological sleepiness increases. MSLT is sensitive to both trait and state level of CNS arousal (Littner et al 2005; Arand et al 2005).

MSLT will be used during screening to confirm moderate to severe sleepiness during night shift in SWD patients. It will also be performed after study drug administration to measure LML134 effect on wakefulness.

Screening MSLT will be performed locally at each site by a sleep technologist experienced in the procedure using the same approach as implemented for the efficacy MSLT. The screening MSLT results will be reviewed and scored locally by an experienced sleep expert (such as a sleep medicine specialist).

Post dose MSLT will be performed at time points specified in the Assessment schedule locally at each site by a sleep technologist experienced in the procedure. The results will be scored by a central reader.

The parameters measured and recorded will be the same for the efficacy (post dose) and the screening MSLT, i.e. start and end times of each nap or nap opportunity, latency from lights out to the first epoch of sleep for each nap, and number of sleep-onset REM periods.

See the SOM for details.

8.5.2 Clinical Outcome Assessments (COAs)

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Physical Examination

See Site Operations Manual for details.

8.6.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

8.6.3 Height and weight

- Height
- Body weight
- Body mass index (BMI) will be calculated as (Body weight (kg) / [Height (m)]^2)

8.6.4 Laboratory evaluations

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should be contacted.

8.6.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, reticulocyte count, white blood cell count with differentials (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes presented as % of total white blood cell count and as absolute concentrations), and platelet count will be measured. Coagulation testing including prothrombin time (PT) also reported as INR and activated partial thromboplastin time (aPTT) will be measured.

8.6.4.2 Clinical Chemistry

Sodium, potassium, calcium, magnesium, chloride, creatinine, BUN/urea, uric acid, albumin, CRP, alkaline phosphatase, total bilirubin, bicarbonate/HCO_3, LDH, GGT, AST, ALT, amylase, lipase, CK, glucose, total cholesterol, triglycerides, thyroid stimulating hormone (TSH).

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

8.6.4.3 Urinalysis

Dipstick measurements for protein, blood, and WBC/leukocytes will be performed. If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts, furthermore the protein-creatinine ratio (PCR) and the albumin-creatinine ratio (ACR) will also be measured.

8.6.5 ECG evaluation

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTc

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

As applicable, QTcF and QTcB may be calculated in-house. Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening and/or Baseline visit(s) (as applicable) to assess eligibility. See the Site Operations Manual for additional details.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.6 Pregnancy and assessments of fertility

Pregnancy Testing

Pregnancy tests are required of all female subjects regardless of age or reported sterilization. The result of this test must be received before any female subject may be dosed. See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test requires that study treatment cannot be initiated in either period or has to be immediately interrupted until serum β-hCG is performed and found to be negative.

Refer to Section 9.6 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at Screening/Baseline.

8.6.7 Polysomnography

PSG is the gold standard method to evaluate sleep. In the present study, PSG will be performed at Screening to exclude any other sleep disorder than SWD. Screening PSG will be scored locally at each site by personnel experienced in the procedure (such as sleep technologist and sleep specialist). PSG will also be performed during the daytime sleep following the first dose of LML134 in each treatment period to assess any effect of LML134 on sleep. Post dose PSG will be scored centrally.

Technical details of PSG are specified in the SOM.

8.6.8 Neurological Examination

Neurological assessments will be performed at time points specified in the Assessment schedule to investigate the potential effect of the study drug on gait, coordination, tremor, muscle tone and biceps reflexes. Pre and post dose assessments should be conducted by the same study physician wherever possible.

Details of the examination and scoring of the responses are specified in the SOM.

8.7 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Site Operations Manual regarding sample collection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

PK samples will be obtained and evaluated in all subjects, except the samples collected during treatment with placebo.

LML134 will be determined in plasma by a validated LC-MS/MS method; the anticipated Lower Limit of Quantification (LLOQ) is 0.02 ng/mL. Concentrations will be expressed in mass per volume units and will refer to the free base.

Concentrations below the LLOQ will be reported as "zero" and missing data will be labeled as such in the Bioanalytical Data Report. Concentrations below the LLOQ will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters (with the exception of the pre-dose samples).

The PK blood collection log and sample labeling and shipment instructions are provided in the Site Operations Manual.

Conventional PK parameters will not be calculated due to the limited sampling schedule. However, plasma concentrations will be listed and summary statistics for concentrations will be provided for plasma. The data will be part of the over-all Population PK model.

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after *providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade
   mild: usually transient in nature and generally not interfering with normal activities
   moderate: sufficiently discomforting to interfere with normal activities
   severe: prevents normal activities
2. its relationship to the study treatment
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

AEs will be collected in the CRF for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH-E2D Guideline 2003).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH-E2D Guideline 2003).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 15-1-Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1-Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2-Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include

- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the Dosing Log CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dosing Log CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

Women who are considered to be of child-bearing potential, are required to use highly effective contraception and an additional barrier method, if they are enrolled in this study, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO& PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior. The C-SSRS must be administered at each visit, including unscheduled visits.

The C-SSRS, which uses a semi-structured interview to probe subject responses, will be administered by an individual who has received training and certification in its administration. At the first study visit, the "baseline/screening" version of the C-SSRS will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject's lifetime and during a predefined period. At subsequent visits, the "since last visit" version will be administered.

If, at any time after screening and/or baseline, the score is "yes" on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or "yes" on any item of the Suicidal Behavior section, the subject must be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

In addition, all life-threatening events must be reported as SAEs. For example, if a subject answers "yes" to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of "Non-Suicidal Self-Injurious Behavior" (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior must be reviewed by the Safety Management Team or Early Project Teams.

9.8 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource or eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

Novartis staff or CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff or CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

The post dose PSG and MSLT data will be analyzed by a central reading vendor and provided to Novartis via electronic data transfer.

At the conclusion of the study, the occurrence of any emergency code breaks will be determined after return of all code break reports and unused drug supplies to Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set will include all subjects that received any study drug and had any post-baseline assessment.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that impact on PK data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

All available data under safety analysis set will be used for reporting purpose.

11.3 Treatments

Data for study drug administration and concomitant therapies will be listed by treatment sequence and subject.

All available data under safety analysis set will be used for reporting purpose.

11.4 Analysis of the primary variable(s)

The mean of multiple sleep latency scores is the primary variable of this study.

11.4.1 Primary Variable(s)

Each subject will undergo a sleep latency test assessment at each period, at approximately 1:30, 3:30, 5:30 and 7:30 in Day 2 (Night 1) and Day 3 (Night 2) (Days 12 and 13 in Treatment Period 2). The mean value of all the sleep latencies from a subject within a period will be defined as mean sleep latency score for that subject for that period.

11.4.2 Statistical model, hypothesis, and method of analysis

Nicotine is a powerful substance to stimulate wakefulness and attention. At same time screening MSLT reflects the stage of severity of shift work disorder patients. Therefore both smoking status (/nicotine intake) and MSLT at screening will be considered as covariates in the model.

For statistical analysis purposes; subjects under full analysis set with all available MSLT information from both the periods will be included in the analysis.

Mean sleep latency score data will be analyzed using a mixed effect ANOVA model with treatment smoking status at screening, screening MSLT, treatment interaction with screening MSLT and smoking status and period as fixed effects and subject as a random effect. Least square estimates for each treatment and treatment difference (LML134 vs placebo) along with 95% confidence interval will be reported. In studies with short treatment duration in SWD patients or healthy shift workers the usual approach is to compare post-dose conditions and not change from baseline. The reason for this approach is the high variability in MSLT (average of at least three tests is needed as baseline) and that baseline and post-dose MSLT results need to be time matched, as MSLT results depend on circadian rhythm.

The following assessments will be performed to judge efficacy of LML134:

a. Statistical significance: One sided (superiority) p-value of LML134 vs placebo from above fitted ANOVA model will be reported.

A p-value <0.1 will be considered as a positive sign for statistical significance.

b. Estimate of treatment difference (LML134 vs Placebo) will be reported.

An estimate of treatment difference > 1 minute would be considered as significant.

In addition from the above model, effect of LML over placebo in each subgroup (smoking status and MSLT (<6 and >=6)) will be estimated through 95% CI of interaction effects.

Same analysis will be performed at interim.

Graphical display:

Subjects under safety analysis set will be used for reporting. For a thorough investigation of sleep latency time profiles, data from LML134 and placebo will be superimposed using suitable graphical tools like boxplot or arithmetic mean (SD) statistics.

Descriptive summary:

Subjects under safety analysis set will be used for reporting. Sleep latency data will be summarized by treatment and time point. Summary statistics like N, mean, SD, CV, and range will be reported.

11.4.3 Handling of missing values/censoring/discontinuations

If a subject has missing data at any timepoint during night 1 the corresponding timepoint from night 2 will be used to impute the value and vice versa. If a subject has a timepoint missing for both night 1 and 2 then MSLT will be calculated over all the available time points.

11.4.4 Sensitivity analyses

Mean of multiple sleep latency score is essentially a positive outcome. Thus a supportive analysis will be performed using log transformed mean sleep latency scores. Log transformed mean sleep latency score data will be analyzed using a mixed effect ANOVA model with treatment and period as fixed effects and subject as a random effect. Least square estimates for each treatment and treatment difference (LML134 vs placebo) along with 95% confidence interval will be back transformed to report in original scale.

11.4.5 Supportive analysis

The analysis explained in Section 11.4.2 will be performed in a Bayesian platform with non-informative priors for treatment effects. The probability of treatment difference more than 0 and 1 will be reported to assess the similarity with primary analysis.

Futility Analysis:

The same analysis will be performed during interim analysis. The predictive distribution of treatment effect given the available data at interim will be evaluated to assess the chance of meeting proof of concept criteria at the end of complete trial. Explicit decision criteria for interim will be discussed in statistical analysis plan.

11.5 Analysis of secondary variable(s)

Overall safety profile is assessed by AEs, laboratory data, and ECG. Additionally, pharmacokinetics and MSLT scores are assessed under safety.

11.5.1 Efficacy / Pharmacodynamics

Subjects with all available MSLT assessments from both the periods under full analysis set will be used for reporting.

Here we want to take a look at sleep latency more vividly; i.e. rather than looking at overall score we need to look at the score of each time point separately.

Each subject will undergo a sleep latency test assessment at each period, at approximately 1:30, 3:30, 5:30, and 7:30 in Day 2 (Night 1) and Day 3 (Night 2) (Days 12 and 13 in Treatment Period 2). The mean value of sleep latencies averaged over two consecutive nights for each time point for each subject in each period will be defined as sleep latency score for that time point for that subject.

An arithmetic mean +/- SD time profile (time-points: 1:30 AM, 3:30 AM, 5:30 AM, and 7:30 AM) plot will be provided for each treatment. A summary table will be created to report n (number of evaluable subjects), mean, SD, and range for each treatment at each time point.

A mixed model repeated measure analysis of variance will be performed over mean sleep latency scores with treatment, period, time, and treatment*time as fixed effects; correlated observations coming from the same subjects will be adjusted using a subject level random effect and suitable covariance structure. The overall treatment effect for LML134 vs placebo will be reported along with a 95% CI.

11.5.2 Safety

All analysis will be performed under safety analysis set.

Vital signs

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged.

Summary statistics of height, weight, temperature, blood pressure, and pulse rate will be provided by treatment and visit/time using statistics like N, mean, median, standard deviation, and range.

The same data will be plotted using arithmetic mean-SD graphs over time for each parameter separately. Separate lines will be drawn for each treatment in order to see any potential differences.

ECG evaluations

All ECG data will be listed by treatment group, subject, and visit/time, and abnormalities will be flagged.

Each ECG parameter will be summarized by treatment, visit/time using statistics like N, mean, median, standard deviation, and range.

The same data will be plotted using arithmetic mean-SD graphs over time for each parameter separately. Separate lines will be drawn for each treatment in order to see any potential differences. Reference lines will be drawn for normal ranges (if available).

Clinical laboratory evaluations

All laboratory data (hematology, blood chemistry, urinalysis) will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged.

Each laboratory parameter (hematology, blood chemistry, urinalysis) will be summarized by treatment, visit/time using statistics like N, mean, median, standard deviation, and range.

The same data (hematology, blood chemistry, urinalysis) will be plotted using arithmetic mean-SD graphs over time for each parameter separately. Separate lines will be drawn for each treatment in order to see any potential differences. Reference lines will be drawn for normal ranges (if available).

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment.

Furthermore, risk ratio of LML134 compared to placebo along with 95% confidence interval will be drawn in a forest-plot for each system organ class and preferred term.

An adverse event starting in one epoch and continuing into the next epoch is counted only in the onset period. A subject with multiple adverse events within a body system and treatment epoch is only counted once towards the total of this body system and treatment.

Other safety evaluations

All safety data will be listed by treatment, subject, and visit/time. Summary statistics for specific parameters will be reported based on clinical decision. Details of reporting will be mentioned in SAP.

Analysis of PSG data will be discussed in detail in SAP.

11.5.3 Pharmacokinetics

Analysis will be performed under PK analysis set.

LML134 plasma concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Conventional PK parameters will not be calculated due to the limited sampling schedule. However, plasma concentrations will be listed and summary statistics for concentrations will be provided for plasma. The data will be part of the over-all Population PK model.

Concentrations below the LLOQ will be treated as zero in summary statistics for concentration data only. They will not be considered for calculation of PK Parameters (with the exception of the pre-dose samples).

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Not applicable.

11.5.5 Other assessments

Not applicable.

11.7 Sample size calculation

It is planned to have data for 36 subjects with evaluable results under the primary endpoint without any major protocol deviations. Assuming a 20% drop-out rate we expect to enroll approximately 46 subjects. In case there will be less than 36 evaluable subjects additional subjects may be enrolled.

Based on Czeisler et al 2005 a 2 minute increase in primary endpoint for SWD patients compared to placebo is considered to be the 'true effect'. Furthermore a SD of 4 minutes and a 20% drop out rate is used based on other sleep disorder study experience.

Efficacy criteria:

a. Statistical significance: A significant increase compared to placebo in sleep latency characterized by p-value < 0.1

And

b. At least 1 minute increase in MSLT sleep latency compared to placebo characterized by an estimated mean difference of > 1 minute

Sample size is evaluated based on a simulation exercise with an ANOVA model with treatment and period as fixed effects. The following operating characteristics are observed:

Table 11-1 Operating characteristics for dual criteria

True effect* (in mins)	Both criteria met (%)	Both criteria failed (%)	One of the criteria met (%)
1.0	41.3	50.0	8.7
1.2	49.7	41.6	8.7
1.5	62.2	29.8	8.0
1.7	69.9	22.9	7.2
2.0	**80.0**	**14.4**	**5.6**
2.2	85.4	10.2	4.5
2.5	91.5	5.6	2.9

* True effect: Change in MSLT (LML134X-Placebo)

Futility Analysis:

An interim analysis is planned at mid-way with 18 completers to evaluate the chance of attaining proof of concept at the end of the trial. A very low chance may result in early stoppage of the trial due to futility.

11.8 Power for analysis of key secondary variables

No power analysis was performed for secondary variables.

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

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15 Appendix 1: Liver Event Definitions and Follow-up Requirements

Table 15-1 Liver Event Definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	**Actions required**
Potential Hy's Law case ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance*
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance*

Criteria	Actions required
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance*

*Liver event guidance for CRF completion is available in the Site Operations Manual

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase > 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

* Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.