Randomized, Double-blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough (RELIEF)

Protocol Number:	*BUS-P2-01*
Sponsor Project Number:	*CL-5937-02*
Investigational Product:	BLU-5937
Phase of Development:	II
[redacted]	[redacted]

COMPLIANCE

The study will be conducted in accordance with standards of Good Clinical Practice, as defined by the International Council on Harmonisation and all applicable federal and local regulations.

Protocol Version	Date
5.0	***26/SEP/2019***

A Randomized, Double-blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough.

[redacted]

A Randomized, Double-blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough.

I have carefully read this study protocol and agree it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol and in accordance with GCP and the applicable regulatory requirements.

A Randomized, Double-blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough.

On behalf of the sponsor, I am aware of, and agree to comply with, all the procedures contained within this protocol.

[redacted]

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND ACRONYMS

ACCP	American College of Chest Physicians
ACE	Angiotensin-converting-enzyme
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATP	Adenosine triphosphate
BID	bis in die (twice per day)
BMI	Body Mass Index
BPM	Beats Per Minute
BTS	British Thoracic Society
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CRF	Case Report Form
CRO	Contract Research Organisation
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ET	Early Termination
EOS	End of Study
EU	European Union
DBP	Diastolic Blood Pressure
FDA	Food and Drug Administration
FEV1/FVC	Tiffeneau – Pinelli Index
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GGT	Gamma-glutamyl transferase
gm/dL	Grams per deciliter
GMP	Good Manufacturing Practice
h	Hour
HDPE	High-density polyethylene
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IRB	Institutional Review Board
ITT	Intention to Treat
IUD	Intrauterine Device
kg	Kilogram
L	Liter
LCQ	Leicester Cough Questionnaire
LFT	Liver Function Tests
ln	Neperian log transformation

MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
min	Minute
mL	Milliliters
mmHg	Millimetre of Mercury
NASH	Non-alcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Level
OTC	Over-the-counter
pH	The Logarithm, On The Base 10, of The Reciprocal of The Hydrogen Ion Concentration
PI	Principal Investigator
PIL	Participant Information Leaflet
PK	Pharmacokinetic
PR	Time between P and R wave
PT	Preferred Term
QC	Quality Control
QTc	QT Interval Corrected for Heart Rate
QTcF	QT Interval Corrected for Heart Rate – Friderica's Correction Formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SoA	Schedule of Activities
SGOT	Aspartate Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
SOP	Standard Operating Procedure
SRC	Safety Review Committee
ST	ST segment of the Electrocardiogram
SUSAR	Suspected Unexpected Serious Adverse Event
T	T wave of the Electrocardiogram
UCAS	Upper Airway Cough Syndrome
ULN	Upper Limit of Normal
USA	United States of America
UK	United Kingdom
VAS	Visual Analogue Scale

STUDY SYNOPSIS

Name of Sponsor/Company:	Bellus Health Inc.
Name of Product:	BLU-5937
Title of Study:	A Randomized, Double-blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough
Short Title/Acronym:	*RELIEF*
Study Development Phase:	II
Study Centres:	Approximately 15 sites in the UK and USA
Objectives & Endpoints:	**Objectives:** • The primary objective of this study is to assess the efficacy and safety of BLU-5937 for the treatment of unexplained or refractory chronic cough • The secondary objective is to establish the optimal therapeutic doses for the Phase 2b/3 studies **Primary Efficacy Endpoint** • Change from baseline in awake cough frequency (cough recorder) at end of each dose level **Secondary Efficacy Endpoints** • Change from baseline in 24-hour cough frequency (cough recorder) at end of each dose level and follow up • Change from baseline in awake cough frequency (cough recorder) at follow up • Change from baseline in cough severity as measured with VAS at end of each dose level and follow up • Change from baseline in Leicester cough questionnaire total score at end of each treatment period • Global Rating of Change Scale at end of each dose level and follow up **Exploratory Efficacy Endpoints** [redacted]
Safety Endpoints	**Safety Endpoints** • Adverse Event (AE) reporting • Spontaneous taste disturbance AE reporting (subjects will complete a questionnaire on type, severity and duration of taste disturbance AEs)

<table>
<tr><td></td><td>
• Relationship between incidence of taste AEs and BLU-5937 systemic exposure (pre dose and 1 hour post dose)
• Vital signs, ECG
• Clinical Laboratory
• Physical exam
Pharmacokinetics
• BLU-5937 plasma levels (pre dose and 1 hour post dose)
</td></tr>
<tr><td>Investigational product, Dose, and Mode of Administration (proposed):</td><td>
BLU-5937
25, 50, 100, 200 mg BID administered as 25 mg tablets (for the 25, 50, 100 mg BID dose levels) or 200 mg tablets (for the 200 mg BID dose level). BID dosing means every 12 hours, +/- approximately 1 hour. [redacted]
</td></tr>
<tr><td>Placebo, Dose, and Mode of Administration:</td><td>
Placebo-to-match appearance of BLU-5937 25 mg & 200 mg tablets
Manufacturer: [redacted]
Mode of administration: oral
</td></tr>
<tr><td>Study Design:</td><td>
This is a randomized, double-blind, placebo-controlled, two-period crossover, dose escalation study of BLU-5937 in subjects with unexplained or refractory chronic cough.
Subjects will be screened during a period of up to 14 days and undergo screening cough monitoring. Approximately 68 subjects who meet entry criteria will be randomized into the study. There will be two 16-day treatment periods (BLU-5937 or placebo) with a 10-14 days washout period between treatments. BLU-5937 will be administered in a dose escalation manner as follows:
<table>
<tr><th><u>Study Day*</u></th><th><u>BLU-5937 Dose/Placebo</u></th></tr>
<tr><td>Period 1 (Days 1-4) or
Period 2 (Days 31-34)</td><td>25 mg BID or Placebo BID</td></tr>
<tr><td>Period 1 (Days 5-8) or
Period 2 (Days 35-38)</td><td>50 mg BID or Placebo BID</td></tr>
<tr><td>Period 1 (Days 9-12) or
Period 2 (Days 39-42)</td><td>100 mg BID or Placebo BID</td></tr>
<tr><td>Period 1 (Days 13-16) or
Period 2 (Days 43-46)</td><td>200 mg BID or Placebo BID</td></tr>
</table>
**this assumes a 14-day wash out period*

Subjects will be administered study drug orally (first dose to be taken on the morning of Day 1 for period 1 and on the morning of Day 31 for period 2). There is no flexibility in visit window for Treatment visits; each dose is to be taken for 4 days.
The following assessments will be conducted to evaluate the efficacy of BLU-5937:
• ***Objective Cough Frequency*:** 24-hour cough recording at Screening (Day -14 to -1), Baseline Period 1 (Day 0) and on Days 4, 8, 12, 16, 30 (Baseline Period 2), 34, 38, 42, 46, and 60 (Follow Up) using a custom-built digital recording device (VitaloJAK, Vitalograph, Ltd)
</td></tr>
</table>

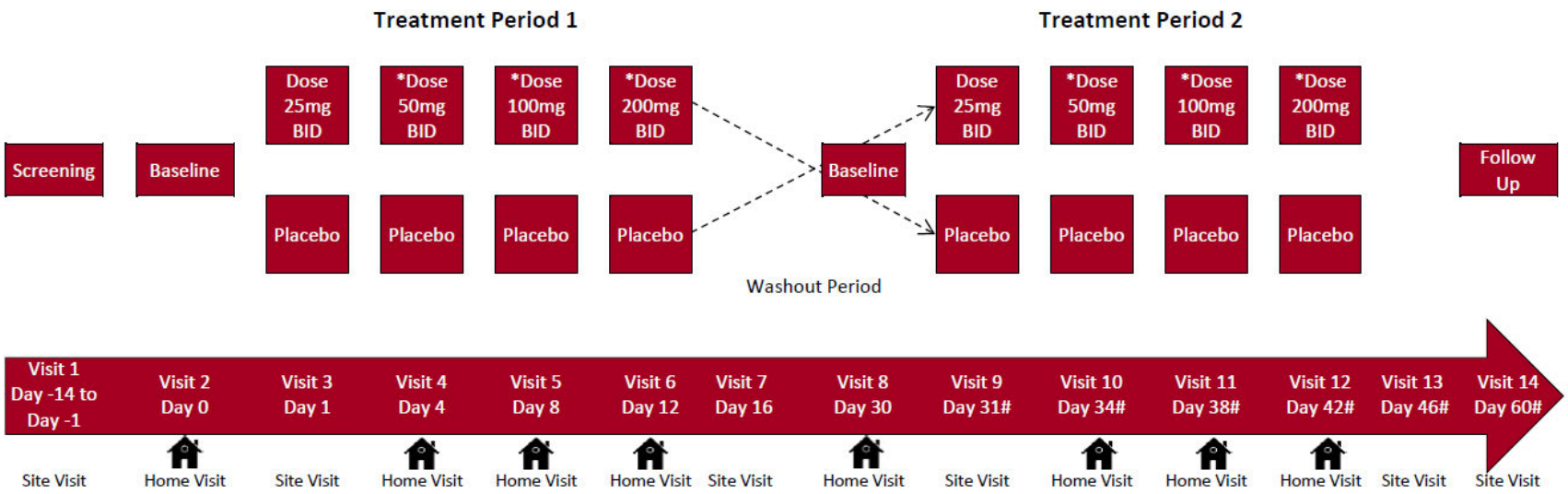
	• ***Cough Severity Visual Analogue Scale (VAS)*:** scored on a 100 mm visual analogue scale at Screening (Day -14 to -1) subject to record cough severity over past 2 weeks, Baseline (Day 0) and on Days 4, 8, 12, 16, 30 (Baseline Period 2), 34, 38, 42, 46 and 60 (Follow Up) subject to record cough severity over past 24 hours • ***Leicester Cough Questionnaire (LCQ):*** completed on Days 1, 16, 31, and 46. • ***Global Rating of Change Scale:*** scored at Days 4, 8, 12, 16, 34, 38, 42, 46 and 60 (Follow Up) Subjects will return 10-14 days after completing the second Treatment Period (Day 46/Early Withdrawal) for a Follow-Up Visit (Day 60) to assess cough count and AEs
Duration of Treatment and Subject Confinement:	Duration of clinical trial (per subject) up to 74 days: Screening – 1 to 14 days Treatment Period 1 – 16 days Wash out – 10 to 14 days Treatment Period 2 – 16 days Follow up – 10 to 14 Days
Safety Assessments:	Safety will be assessed through monitoring of adverse events (AEs), physical examination, vital signs, electrocardiograms (ECGs), and laboratory assessments. Frequency of assessments is detailed in the Schedule of Activities (Table 1)
Study Population:	Male and female patients (18-80 years of age inclusive) with unexplained or refractory chronic cough
Planned Number of Subjects:	Approximately 68 subjects may be randomized in the study in order to achieve 62 completers
Inclusion Criteria:	Subjects who meet all of the following criteria will be included in the study: 1. Have provided written consent and are willing and able to comply with all aspects of the protocol. 2. Women and Men between 18 and 80 years of age inclusive. 3. Chest radiograph or CT thorax within the last 5 years from screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough in the opinion of the Principal Investigator and Medical Monitor. 4. Have unexplained or refractory chronic cough for at least one year: a cough that is unresponsive to at least 8 weeks of targeted treatment for identified underlying triggers including reflux disease, asthma and post-nasal drip or unexplained cough; or a cough for which no objective evidence of an underlying trigger can be determined after investigation (see Appendix 1). 5. Awake Cough Count of ≥ 10 per hour (Cough Count at Screening). 6. A score of ≥ 40mm on the Cough Severity VAS at Screening. 7. Women of child-bearing potential must have a negative serum pregnancy test at Screening. 8. Women of child-bearing potential must use a highly effective contraception method from Screening through to the Follow-Up Visit. Acceptable birth

	control methods include: a. Intrauterine device (IUD) or intrauterine system (IUS); b. Tubal ligation; or male sterilization. c. When in line with the preferred life style of the subject, true and complete abstinence (not periodic abstinence) is acceptable. For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal; a postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female. [redacted] 9. Male subjects and their partners of child-bearing potential must use 2 methods of acceptable birth control (one method as listed in Inclusion Criteria 8), 1 of which must be a barrier method, and make no donation of sperm from Screening until 3 months after the last dose of study drug.
Exclusion Criteria:	Subjects are NOT eligible for this study if they meet any of the following criteria: 1. Current Smoker or Vaper. 2. Individuals who have given up smoking or vaping within the past 6 months, or those with >20 pack-year smoking history. 3. Diagnosis of COPD, bronchiectasis, idiopathic pulmonary fibrosis based on clinician assessment. *4. Criteria No.4 removed from here in protocol v5.0. See Table 2 section 4.4 for details.* 5. FEV1/FVC < 60%. 6. History of upper respiratory tract infection or recent significant change in pulmonary status within 4 weeks of the Baseline/Visit 2 (Day 0). *7. Criteria No.7 removed from here in protocol v5.0. See Table 2 section 4.4 for details.* 8. Requiring concomitant therapy with prohibited medications or non-pharmacological therapy (see Table 2, Section 4.4). 9. Medical history of hypogeusia/dysgeusia or known presence of a dysfunction in his/her ability to taste. 10. History of concurrent malignancy or recurrence of malignancy within 2 years prior to Screening (not including subjects with <3 excised basal cell carcinomas). 11. History of a diagnosis of drug or alcohol dependency or abuse within the last 3 years. 12. Any condition possibly affecting drug absorption (e.g., gastrectomy,

	gastroplasty, any type of bariatric surgery, vagotomy, or bowel resection). 13. Screening systolic blood pressure (SBP) >160 mm Hg or a diastolic blood pressure (DBP) >100 mm Hg. 14. Clinically significant abnormal electrocardiogram (ECG) at Screening, including any of the following: a. QTcF interval > 450 milliseconds b. Atrial fibrillation or atrial flutter c. Heart rate <40 beats per minute >110 bpm d. Second degree or third degree (complete) AV block e. Left bundle branch block (including hemiblock) f. Wolff-Parkinson-White Syndrome Personal or family history of congenital long QT syndrome or family history of sudden death 15. Clinically significant abnormal laboratory tests at Screening, including: a. Alkaline phosphatase (ALP), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT) >150% of the upper limit of normal (ULN), gamma-glutamyl transferase (GGT) >200% of the upper limit of normal (ULN), or Total bilirubin above the upper limit of normal (ULN) b. Creatinine >200% of the upper limit of normal (ULN) c. Unexplained creatine kinase concentration >3 x ULN d. haemoglobin < 10 g/dL, WBC count <2500 mm3, neutrophil count <1500 mm3, platelet count <100 × 103/mm3 e. Positive screen for drugs of abuse (certain drugs of abuse are acceptable for non-cough indications see section 4.4) 16. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) or international normalized ratio (INR) of ≥1.5. *17. Criteria No.17 removed from here in protocol v5.0. See 15c above for details.* 18. Breastfeeding. *19. Criteria No.19 removed from here in protocol v5.0. See Table 2 section 4.4 for details.* 20. Blood donation within 56 days or plasma donation within 7 days prior to dosing. 21. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the Investigator or

	Sponsor, would make the subject inappropriate for entry into this trial.
Prohibited Medications or non-pharmacological Therapies	Refer to Table 2 in Section 4.4.
Statistical Analysis:	**Efficacy Analyses** Primary Endpoint A repeated measures mixed model analysis of variance will be used to evaluate the primary endpoint. The log transformed awake cough frequency measured at assessment visits within periods will be the repeated measure. The model will include fixed effect terms for treatment sequence, treatment, period as well as assessment visit within period and the treatment by assessment visit interaction. Average log baseline awake cough count and period specific log baseline awake cough frequencies will be included as covariates. Subject will be classed as a random effect. Model contrasts will be constructed to compare active treatment to placebo for each dose level. Secondary Endpoints Statistical approaches for analysis of the secondary endpoints will be similar in approach to that of the primary endpoint. Safety Endpoints Safety endpoints will be summarized by treatment group and, where appropriate, by dose and timepoint.

Figure 1. Schedule of Visits



Screening Window: Days -14 to Day 0
Washout Period: 10 to 14 days
Follow Up Period: 10 to 14 days

* When a new dose is dispensed it is to be started the following morning, after removal of the VJAK.
# Days in Treatment period 2 assume a 14 day washout & 14 day follow-up period.

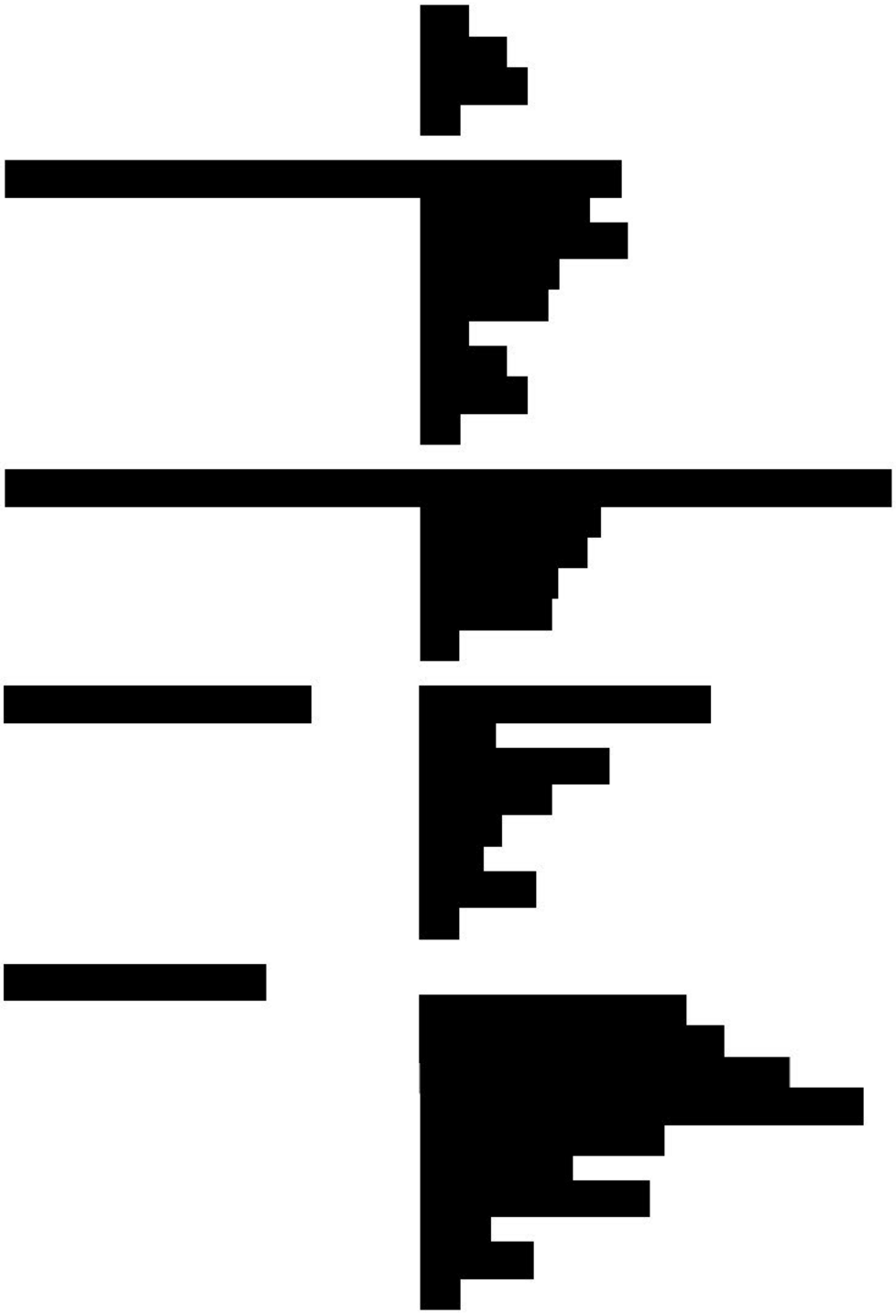
Table 1. Schedule of Activities

Procedure	Visit 1 Screening[A, B] Day -14 to -1	Day -4 to Day 1 Randomization in [redacted]	Visit 2 & 8 Day 0[D] & Day 30[D] (Baseline)	Visit 3 & 9 Day 1 & Day 31[C]	Visit 4 & 10 Day 4[D] & Day 34[D]	Visit 5 &11 Day 8[D] & Day 38[D]	Visit 6 & 12 Day 12[D] & Day 42[D]	Visit 7 & 13 Day 16 & Day 46 / Early Termination	Visit 14 Follow Up Day 60
Written Informed Consent	X								
Inclusion/Exclusion Criteria	X			X[I]					
Randomization [redacted]		X*		(X)**					
Allocate treatment period 2 kit (in [redacted]				X[P]					
Demographics, Medical History & Medication History	X								
Review of Chest Radiograph/CT Thorax from the past 12 months[E]	X								
VAS[N]	X		X		X	X	X	X	X
Height, & Weight & BMI	X								
Vital Signs (BP, HR, RR, Temperature)	X			X	X	X	X	X	X
Complete Physical Exam	X							X	
Brief Physical Exam[N]				X					X
12-lead ECG (at screening & pre-dose)	X			X	X	X	X	X	
12-lead ECG (1-hour post morning dose)				X	X	X	X	X	
Spirometry	X								
Clinical Laboratory (Biochem/Haemo)	X			X				X	
LFT Panel (bilirubin total, bilirubin direct and indirect, ALP, AST, ALT, GGT) only)	X			X	X	X	X	X	
Lipids (TC, HDL-C, LDL-C, TGs)				X				X	
Coagulation (PT,INR,aPTT)	X			X	X	X	X	X	
Serum Pregnancy Test[K]	X								
Urine Pregnancy Test[K, N]				X				X	
Urine Drug Screen[M]	X			X				X	
Urinalysis (w/Microscopy[F])	X			X				X	
Attach Cough Monitor[G]	X		X		X	X	X	X	X
Collect Cough Monitor	X[H]			X	X[H]	X[H]	X[H]	X[H]	X[H]
LCQ[N]				X				X	
Global Rating of Change Scale[N]					X	X	X	X	X
Concomitant Medications	X		X	X	X	X	X	X	X

Adverse Event			X	X	X	X	X	X	X
Taste Effects Questionnaire[L]			X[O]	X	X	X	X	X	X
Procedure	**Visit 1 Screening[A, B] Day -14 to -1**	**Day -4 to Day 1 Randomization**	**Visit 2 & 8 Day 0[D] & Day 30[D] (Baseline)**	**Visit 3 & 9 Day 1 & Day 31[C]**	**Visit 4 & 10 Day 4[D] & Day 34[D]**	**Visit 5 &11 Day 8[D] & Day 38[D]**	**Visit 6 & 12 Day 12[D] & Day 42[D]**	**Visit 7 & 13 Day 16 & Day 46 / Early Termination**	**Visit 14 Follow Up Day 60**
Dispense Study Medication &/or Accountability				X	X	X	X	X	X
Plasma PK Sample [J]				X	X	X	X	X	
[redacted]				X					

A: Multiple Screening Visits may be required to complete all screening assessments
B: The Screening Period may be extended beyond 14 days if required and approved by the Medical Monitor (e.g. additional follow-up on findings from any of the Screening assessments)
C: Washout period may be 10-14 days to allow for flexible scheduling. Days in the table are based on a 14-day washout period. The Washout Period may be extended beyond 14 days if required and approved by the Medical Monitor.
D: Visits may be conducted at subjects' home (by Mobile Research Nurse)
E: If not done within the past 12 months patient is ineligible
F: Microscopy to be performed only if clinically indicated
G: Cough monitor should be attached before 10am, pre-dose and worn for 24 hours during each assessment.
H: Cough monitor to be returned to site by courier by the subject after 24-hour recording
I: Visit 3/Day 1 only
J: PK samples taken pre-dose [redacted]
K: For Women of Childbearing Potential
L: Completed only if taste AEs are reported
M: Subjects who test positive may be re-tested if consumed poppy seeds on bread products
N: To be completed before morning dose
O: Visit 8/Day 30 only
P: Visit 9/Day 31 only. [redacted].
[Randomization] * triggers shipment of additional treatment kits to the site.
[Randomization] **At visit 3/Day 1 if not already completed;
[Initial shipment of IP to a site is triggered [redacted] once the first subject has started screening].

INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE



1. INTRODUCTION

Cough represents an essential defensive mechanism for the airways by preventing inhalation or aspiration of harmful gases or particles from the environment. It also helps mucous clearing from the lower respiratory tract. However, cough can also be a sign of many inflammatory diseases of the respiratory tract. Cough represents one of the most frequent complaints leading patients to seek medical attention (Schappert, 2006). In cough guidelines, such as those published by the American College of Chest Physicians and the British Thoracic Society (Irwin, 2006; Morice, 2006), cough is characterized by the length of time a patient is coughing:

- Acute - up to 3 weeks,
- Sub-Acute - from 3 to 8 weeks,
- Chronic - greater than 8 weeks.

Patients who present to a physician for a persistent cough are evaluated and treated for obvious and common causes of cough. If a patient continues to cough, he/she is evaluated for conditions that are commonly associated with chronic cough. These include asthma, gastroesophageal reflux disease (GERD), and upper airway cough syndrome (UACS) (Dicpinigaitis, 2011; Morice, 2006). A patient may be evaluated for less common diseases based on the patient's history, other symptoms, or physical findings. Patients in whom no treatable cause of their cough can be found are characterized as having "refractory chronic cough" (Gibson, 2016). The prevalence of chronic cough has been estimated as affecting 11-13% of the population (Ford, 2006; Song,2014). It most commonly appears in the fifth and sixth decades of life, and can persist for years (Morice, 2000; Morice, 2014). Patients are most commonly women (approximately 66%-75% of patients are women). Chronic cough can seriously impair quality of life as it has physical (exhaustion, sleep deprivation, urinary incontinence, vomiting, headache, rib fracture) social (interference with lifestyle and leisure, embarrassment of coughing in public, social exclusion) and psychosocial (depression, frustration, anxiety) consequences with a marked effect on Quality of Life as measured by instruments such as the Leicester Cough Questionnaire (LCQ) (Birring, 2003; Kelsall, 2008). The disabling effects of chronic cough are understandable, given that patients with the condition cough hundreds or even thousands of times per day for months to years (Smith, 2016).

The management of chronic cough is based on the diagnosis and treatment of the underlying disease. However, there are a significant proportion of patients with unexplained or refractory chronic cough who do not respond to treatment of the underlying disease or do not have an underlying condition identified and treatment options for these patients are very limited (Morice, 2006). Patients and clinicians will frequently try over-the-counter agents such as dextromethorphan, guaifenesin, and antihistamines with little benefit. Prescription options in the U.K. include low-dose oral morphine, and in the U.S. include benzonatate, codeine and related opiate products. Studies have evaluated amitriptyline (tricyclic antidepressant) and gabapentin (neuromodulator) (Dicpinigaitis, 2014) with some patients having some benefit but with some significant adverse events (Ryan, 2012). Over-the-counter (OTC) antitussive products that contain antihistamine and/or dextromethorphan are also widely used for cough, but these compounds have limited efficacy.

Importantly, there have been no FDA approvals for a novel pharmaceutical agent to treat cough in over 50 years.

1.1. Cough Reflex Mechanism

Primarily, the cough reflex is mediated by peripheral sensory nerves in the airways. Two main subtypes of sensory vagal afferent nerves are involved in cough reflex. The first subtype is myelinated sub-epithelial Aδ fibers that are found in the upper airways and respond to mechanical stimuli (mechanoreceptors) and rapid change in pH. It is fast conducting and is thought to mediate the protection

against acid and foreign body aspiration. The second subtype is C-fibers; these are unmyelinated nociceptive nerves that are sensitive to chemical irritants (chemoreceptors) and endogenous inflammatory mediators (Morice, 2010). C-fibers are thought to be involved in the exaggerated cough experienced in chronic cough. Histological and electrophysiological experiments in the rat and guinea pig revealed that C-fibers innervating the pulmonary system are derived from two distinct vagal sensory ganglia (Undem, 2004): 1) the jugular ganglion neurons, which project C-fibers to the upper airways (larynx, trachea, bronchus) and the lung parenchymal tissue; and 2) the nodose ganglion neurons, which project C-fibers to the structures within the lungs, exclusively.

Vagal C-fibers innervating the airways express P2X3 receptors and can be activated by adenosine triphosphate (ATP) released into the airways. The resulting depolarisation can initiate action potentials that are transmitted centrally and interpreted as urge to cough. P2X3 receptors are ATP-gated ion channels that belong to a family of purinergic receptors. Members of this family assemble as homotrimeric (three subunits of P2X3) and heterotrimeric (two subunits of P2X3 and one subunit of P2X2) ion channels. Furthermore, immunohistochemistry and single cell RT-PCR analysis have shown that C-fibers arising from nodose ganglia expressed both P2X2 and P2X3 subunits while those from the jugular ganglia expressed primarily P2X3 subunits (Kwong, 2008). These data indicate that C-fibers derived from the jugular ganglia are activated primarily by P2X3 homotrimeric receptors, whereas the C-fibers from the nodose ganglia are stimulated by P2X2/3 heterotrimeric receptors.

In chronic cough, the majority of stimuli triggering cough is affecting the upper airways (e.g. strong odour/smoke, cold air, post-nasal drips, aspiration of gastroesophageal reflux, speaking). Furthermore, the greatest concentration of cough receptors is in the larynx, carina and bifurcation of the medium to large-sized bronchi. These observations indicate that the upper airways play a major role in cough. Therefore, given that upper airways are innervated by jugular C-fibers that express primarily P2X3 channels, it suggests that P2X3 homotrimeric receptors are responsible for the increase in cough reflex sensitivity (Undem, 2004; Kwong, 2008).

The role of P2X2/3 receptors in taste function is supported by immunohistochemistry and behavioural taste studies performed in rodents. Immunohistochemical staining of the C-fibers innervating the taste buds of rodents showed the presence of both P2X2 and P2X3 channels colocalized at the C-fibers concentrated in the taste buds, indicating the formation of P2X2/3 receptors (Bo, 1999). Studies of double knock-out mice showed that complete loss in taste function required knock out of both P2X2 and P2X3 channels, suggesting that both channels play an important role in taste signal transduction (Finger, 2005). Therefore, these results support the hypothesis that a drug that would inhibit only P2X3 homotrimeric receptors would have no or minimal impact on taste perception.

1.2. BLU-5937 Pharmacology

BLU-5937, a small molecule of the imidazopyridine chemical class, is a potent, selective and non-competitive P2X3 homotrimeric receptor antagonist. P2X3 receptors are ATP ion-gated channels located on primary afferent neurons. ATP released from damaged or inflamed tissues in the airways acts on P2X3 receptors on primary afferent neurons, triggering depolarisation and action potentials that are transmitted centrally and interpreted as urge to cough. There are preclinical and clinical evidence supporting the role of P2X3 receptors in hypersensitization of the cough reflex, leading to chronic cough. By inhibiting P2X3 receptors on the primary sensory neurons, BLU-5937 would inhibit the hypersensitization of the cough reflex and, hence, the exaggerated cough experienced in chronic cough patients.

1.3. Clinical Indication

BLU-5937 is an investigational drug that is developed for the treatment of unexplained or refractory chronic cough.

1.4. Nonclinical Experience

[redacted]

1.5. Nonclinical Pharmacokinetics

[redacted]

[redacted]

1.6. Toxicology

[redacted]

1.7. Clinical Experience

[redacted]

1.8. Study Rationale

With extensive efforts in animals, one P2X3 antagonist drug has started to validate the mechanism of P2X3 inhibition in cough hypersensitivity in clinical trials, gefapixant (AF-219, MK-7264). In 2014, a proof-of-concept phase II study highlighted a large decrease in cough frequency (75%) with gefapixant 600 mg BID vs placebo in 24 chronic cough patients (Abdulqawi, 2015). Follow-up studies exploring a wide range of doses have indicated a clear dose-response relationship between potent cough suppression and gefapixant administration, indicating promising potential for the P2X3 antagonist in being the first new cough therapy in 60 years.

However, gefapixant's attractive efficacy has been limited by unwanted taste side-effects (dysgeusia, hypogeusia or ageusia). Initial human proof-of-concept study at a high dose of 600 mg twice daily led to clinically significant taste disturbances in all patients that were associated with a 25% dropout rate (Abdulqawi, 2015). Titration to lower doses led to a decrease in the taste side-effects, although these on-target issues could not be resolved as gefapixant still led to significant taste adverse events at effective doses for cough suppression (Sheridan, 2016). The incidence of taste adverse events reported with gefapixant at the predicted therapeutic dose of 50 mg BID was 81% (Smith, 2017). The taste adverse events associated with gefapixant is believed to be due to its low selectivity for P2X3 homotrimeric receptors (involved in cough) versus P2X2/3 heterotrimeric receptors (responsible for taste perception).

Accordingly, a potent, orally bioavailable small molecule antagonist of P2X3 that is highly selective for P2X3 homotrimers versus P2X2/3 heterotrimers such as BLU-5937 would hypothetically limit unwanted taste side-effects while being efficacious in the treatment of chronic cough.

[redacted]

1.9. Risk/Benefit Assessment

1.9.1 Known Potential Risks

[redacted]

1.9.2. Known Potential Benefits

Chronic cough can seriously impair quality of life. The disabling effects of chronic cough are understandable, given that patients with the condition cough up to hundreds of times per hour for months to years. The treatment options of chronic cough are limited and not optimal due to either low efficacy (OTC drugs) or poor tolerance (gabapentanoids/opioids). Subjects recruited in this study may see an improvement in their symptoms. Clinical studies with another P2X3 antagonist (gefapixant) have shown significant reduction in cough frequency in chronic cough patients.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of this study is to assess the efficacy and safety of BLU-5937 for the treatment unexplained, refractory chronic cough.

2.2. Secondary Objective

The secondary objective is to establish the optimal therapeutic doses for the Phase 2b/3 studies.

2.3. Primary Efficacy Endpoint

Change from baseline in awake cough frequency (cough recorder) at end of each dose level.

2.4. Secondary Efficacy Endpoints

- Change from baseline in 24-hour cough frequency (cough recorder) at end of each dose level and follow up
- Change from baseline in awake cough frequency (cough recorder) at follow up

- Change from baseline in cough severity as measured with VAS at end of each dose level and follow up
- Change from baseline in Leicester cough questionnaire total score at end of each treatment period
- Global Rating of Change scale at end of each dose level and follow up

2.5. Exploratory Efficacy Endpoints

- [redacted]

2.6. Safety Endpoints

- Adverse Event (AE) reporting
- Spontaneous taste disturbance AE reporting (subjects will complete a questionnaire on type, severity and duration of taste disturbance AEs)
- [redacted]
- Vital signs
- ECG
- Clinical laboratory
- Physical exam

2.7. Pharmacokinetics

- BLU-5937 plasma levels (pre dose and 1 hour post dose)

3. STUDY DESIGN

This is a Phase 2, multicentre, randomized, double-blind, placebo-controlled, two-period crossover, dose escalation study of BLU-5937 in subjects with unexplained or refractory chronic cough.

Subjects will be screened during a period of up to 14 days and undergo a screening 24-cough monitoring using an objective measure of coughs (VitaloJAK Vitalograph, Ltd.) to exclude the mild cougher subjects (< 10 cough/hr, from awake cough count).

Approximately 68 subjects who meet entry criteria will be randomized into the study. There will be two 16-day treatment periods (BLU-5937 or placebo) with a 10-14 days washout period between treatment periods. Each Period will consist of 4 escalating dose levels. Each dose level will be of 4 days duration.

The duration of treatment for each subject is as follows:

- Screening Period: up to 14 days

- Baseline Period 1: 1 day
- Treatment Period 1 (BLU-5937 or Placebo):
  16 days (escalating doses of 25, 50, 100, 200 mg BID or placebo; 4 days for each dose)
- Washout: 10-14 days
- Baseline Period 2: 1 day
- Treatment Period 2 (Placebo or BLU-5937):
  16 days (escalating doses of 25, 50, 100, 200 mg BID or placebo; 4 days for each dose)
- Follow-Up Period: 10-14 days

Individual subject participation is expected to be approximately 74 days including Screening, Baseline, Treatment periods and Follow-Up period.

3.1. Discussion of Study Design

This randomized, double-blind, placebo-controlled, two-period crossover, dose escalation study design has been previously used to characterize the efficacy and safety of other drugs in patients with unexplained, refractory chronic cough and was deemed acceptable by the Health Authorities in a context of early Phase 2 investigation. This particular study design will allow the testing of several doses in a restricted number of patients in view of gathering initial safety and efficacy data in the target patient population and for the selection of optimal doses to be evaluated in other clinical studies.

4. SUBJECT POPULATION

Subjects who meet all the inclusion criteria and none of the exclusion criteria at the screening visit will be eligible for participation in this study. Continued eligibility will be assessed upon admission to the clinical site at Visit 3 (Day1), prior to the first study drug administration.

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study.

4.1. Inclusion Criteria

Subjects who meet all of the following criteria will be included in the study:

1. Have provided written consent and are willing and able to comply with all aspects of the protocol.
2. Women and Men between 18 and 80 years of age inclusive.
3. Chest radiograph or CT thorax within the last 5 years from screening not demonstrating any abnormality considered to be significantly contributing to the chronic cough in the opinion of the Principal Investigator and Medical Monitor.
4. Have unexplained, refractory chronic cough for at least one year: a cough that is unresponsive to at least 8 weeks of targeted treatment for identified underlying triggers including reflux disease, asthma and post-nasal drip or unexplained cough; or a cough for which no objective evidence of an underlying trigger can be determined after investigation (see Appendix 1).
5. Awake Cough Count of ≥ 10 per hour (Cough Count at Screening).
6. A score of ≥ 40mm on the Cough Severity VAS at Screening.
7. Women of child-bearing potential must have a negative serum pregnancy test at Screening.

8. Women of child-bearing potential must use a highly effective contraception method from Screening through the Follow-Up Visit. Acceptable birth control methods include:
    a. intrauterine device (IUD) or intrauterine system (IUS);
    b. tubal ligation; or male sterilization.
    c. When in line with the preferred life style of the subject, true and complete abstinence (not periodic abstinence) is acceptable.

    For the purposes of this study, a female of childbearing potential is defined as any female who has experienced menarche and is pre-menopausal; a postmenopausal state is defined as no menses for 12 months without an alternative medical cause in a previously menstruating female.

    [redacted]

9. Male subjects and their partners of child-bearing potential must use 2 methods of acceptable birth control (one method as listed in Inclusion Criteria 8), 1 of which must be a barrier method, and make no donation of sperm from Screening until 3 months after the last dose of study drug.

4.2. Exclusion Criteria

Subjects are NOT eligible for this study if they meet any of the following criteria:

1. Current smoker or vaper.
2. Individuals who have given up smoking or vaping within the past 6 months, or those with >20 pack-year smoking history.
3. Diagnosis of COPD, bronchiectasis, idiopathic pulmonary fibrosis based on clinician assessment.
4. *Criteria No.4 removed from here in protocol v5.0. See Table 2 section 4.4 for details.*
5. FEV1/FVC < 60%.
6. History of upper respiratory tract infection or recent significant change in pulmonary status within 4 weeks of the Baseline/Visit 2 (Day 0).
7. *Criteria No.7 removed from here in protocol v5.0. See Table 2 section 4.4 for details.*
8. Requiring concomitant therapy with prohibited medications or non-pharmacological therapy (see Table 2, Section 4.4).
9. Medical history of hypogeusia/dysgeusia or known presence of a dysfunction in his/her ability to taste.
10. History of concurrent malignancy or recurrence of malignancy within 2 years prior to Screening (not including subjects with <3 excised basal cell carcinomas).
11. History of a diagnosis of drug or alcohol dependency or abuse within the last 3 years.
12. Any condition possibly affecting drug absorption (e.g., gastrectomy, gastroplasty, any type of bariatric surgery, vagotomy, or bowel resection).
13. Screening systolic blood pressure (SBP) >160 mm Hg or a diastolic blood pressure (DBP) >100 mm Hg.
14. Clinically significant abnormal electrocardiogram (ECG) at Screening, including any of the following:

a. QTcF interval >450 milliseconds
b. Atrial fibrillation or atrial flutter
c. Heart rate <40 beats per minute >110 bpm
d. Second degree or third degree (complete) AV block
e. Left bundle branch block (including hemiblock)
f. Wolf-Parkinson-White Syndrome
g. Personal or family history of congenital long QT syndrome or family history of sudden death

15. Clinically significant abnormal laboratory tests at Screening, including:
    a. Alkaline phosphatase (ALP), alanine aminotransferase (ALT, SGPT), aspartate aminotransferase (AST, SGOT) >150% of the upper limit of normal (ULN), gamma-glutamyl transferase (GGT) >200% of the upper limit of normal (ULN), or Total bilirubin above the upper limit of normal (ULN)
    b. Creatinine >200% of the upper limit of normal (ULN)
    c. Unexplained creatine kinase concentration >3 x ULN
    d. haemoglobin < 10 g/dL, WBC count <2500 mm3, neutrophil count <1500 mm3, platelet count <100 × 103/mm3
    e. Positive tests for drugs of abuse (certain drugs of abuse are acceptable for non-cough indications see section 4.4)
16. Significant coagulopathy as defined by a known hereditary deficiency of coagulation factors or platelet function or an unexplained elevation of the prothrombin time (PT) or international normalized ratio (INR) of ≥1.5.
17. *Criteria No.17 removed from here in protocol v5.0. See 15c above for details.*
18. Breastfeeding.
19. *Criteria No.19 removed from here in protocol v5.0. See Table 2 section 4.4 for details.*
20. Blood donation within 56 days or plasma donation within 7 days prior to dosing.
21. Other severe, acute, or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the Investigator or Sponsor, would make the subject inappropriate for entry into this trial.

4.3. Withdrawal Criteria

4.3.1. Before First Treatment Administration

Before the first treatment administration, inclusion/exclusion criteria will govern the subjects to be dosed. Subjects who have been screened but who have not been randomized into the study may be re-screened once for participation if approved by the medical monitor and Sponsor e.g. subject has upper respiratory tract infection or has a positive poppy seed drug test at the screening visit. Subjects who do not meet the awake cough count criteria at screening (Awake Cough Count of ≥ 10 per hour) cannot be re-screened.

Awake cough count results must not be rounded. Subjects may not be randomized into the study more than once.

Subjects who report a taste disturbance at Day 0 should not be randomized and should not be re-screened.

4.3.2. After First Treatment Administration

Subjects may, at any time, voluntarily withdraw from the study or be removed from the study at the discretion of the Investigator or Sponsor.

If such withdrawal occurs, or if the subject fails to return for visits, the Investigator should determine the primary reason for a subject's premature withdrawal from the study and record the reason in the subject's study documents.

Attempts should be made to have such subjects complete the EOS/ET assessments. EOS/ET assessments should be performed as soon as possible after the last study treatment administration.

The blind may be broken only in emergency situations, where knowledge of the treatment that the subject received is necessary for safety management (Section 5.2.4).

Details of reasons for removal of subjects will be recorded, reported to the Sponsor and documented in the clinical study report.

For subjects who are lost to follow-up (i.e. those subjects whose status is unclear because they fail to appear for study visits without stating an intention to 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.

4.3.3. Individual Subject Stopping Rules

Possible reasons for discontinuation from the study are:

- The investigator may decide to terminate a subject's participation in the study for safety or administrative reasons e.g. AE, a clinically significant laboratory value, or other medical condition or situation such that continued participation in the study would not be in the best interest of the subject. Appropriate medical measures are to be taken accordingly, and the Sponsor or Sponsor designee is to be notified immediately.
- Subject may be discontinued due to poor study treatment compliance (Section 5.2.6).
- A female subject has a confirmed pregnancy, or, in the case of a male subject, his female partner becomes pregnant.
- At any time during the study a subject may decide to end his/her participation in the study.
- The Investigator or the Sponsor, for any reason, terminates the study.

4.3.4. Liver Function Stopping Criteria

Stopping criteria for an individual subject, after a re-test if needed:

- Any subjects with ALT or AST > 8x ULN
- Any subjects with ALT or AST > 3x ULN and total bilirubin > 2x ULN or INR > 1.5
- Any subjects with ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Note: alternative causes (acute viral hepatitis, hepatobiliary disorders, alcoholic and autoimmune hepatitis, NASH, cardiovascular causes and concomitant treatments that might be responsible for the injury) will have to be eliminated prior to subject discontinuation.

Stopping criteria for entire study:

The study will be temporarily halted if ≥ 1 subject has an increase in ALT or AST > 3x ULN associated with elevation in total bilirubin > 2x ULN and no evidence of obstruction, such as elevated ALP typical of gall bladder or bile duct disease, or malignancy, or impaired glucuronidation capacity caused by genetic (Gilbert syndrome) or pharmacologic (treatment with atazanavir or other drugs) factors, with no other explanation (viral hepatitis, alcoholic or autoimmune hepatitis, other hepatotoxic drugs). If underlying causes are identified, the study may continue if the safety review is supportive. The study will be stopped if no underlying causes are identified.

4.4. Prohibited Medications and non-pharmacological Therapies / Washout

Subjects will be instructed to notify the study site about any new medications taken after the start of the study treatment. Subjects will be asked at each visit if any medications have been taken since their last visit. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject has received the study treatment must be listed in the subject CRF/source documents. The drug name and dose taken will be recorded in the CRF/source documents. Table 2 below outlines all the prohibited medications and non-pharmacological therapies and the washout periods, where applicable before the subject can be enrolled. Investigators are encouraged to contact the study medical monitor if they need to discuss any of the below for advice.

Table 2. Prohibited Medications and non-pharmacological Therapies / Washout Period

Medication	Washout Period / Restrictions
Antitussive Medications / Therapy	
Including but not limited to: dextromethorphan, opioids	Not permitted within 1 week of baseline and prohibited throughout
Gabapentin/pregabalin/baclofen/tricyclics	Should be tapered off safely before stopping and are not permitted within 4 weeks of baseline and prohibited throughout
For Underlying Respiratory Disease / Other Clinical Indications	
Chronic systemic corticosteroid use e.g. Prednisone	Not permitted within 4 weeks of screening and prohibited throughout[$]
Inhaled steroids and antihistamines	Stable dose for at least 4 weeks prior to screening visit and throughout the study
GERD medications e.g. proton pump inhibitors or anti-reflux medications. See exception *	Stable doses for at least 8 weeks prior to screening visit and throughout the study

Neuromodulators e.g. Gabapentin / pregabalin, baclofen, amitriptyline and other tricyclics taken for another clinical indication (not for cough)	Stable dose for at least 8 weeks prior to screening visit and throughout the study
ACE-inhibitor therapy	Not permitted within 12 weeks of screening or throughout the study
Investigational drugs (including P2X3 antagonist)	Not permitted within 60 days of the first dose of study medication or plans to take another within 30 days of study completion
Beta blockers, NSAIDs, and aspirin-containing products	Prohibited if any previous history of bronchospasm with these products
Biologics	Not permitted within 60 days of the first dose of study medication or plans to take another within 30 days of study completion
Physio / Physical / Speech and language Therapy	Only permitted if they have completed a course of the therapy and it will be stable from screening and throughout the study

 # Please contact the Medical Monitor [redacted] to discuss any case

** Alginate therapy is accepted but should not be taken concomitantly with study medication which should be taken an hour before or 2 hours after alginate.*

$ Stopping chronic corticosteroid use should be approved and supervised by a physician before stopping

5. STUDY TREATMENTS

5.1. Investigational Product and Placebo

All doses of the investigational product and placebo will be provided by the sponsor.

5.1.1. BLU-5937 tablets

BLU-5937 (drug product) is manufactured by [redacted] for oral administration. BLU-5937 will be provided as 25 mg and 200 mg tablets.

5.1.2. Placebo

Placebo tablets (25 mg and 200 mg) matched to Sponsor's BLU-5937 investigational product manufactured by [redacted] will be supplied. The excipients in the placebo formulation are identical to the excipients as BLU-5937.

5.2. Investigational Product Management

5.2.1. Packaging, Labelling and Dispensing

The sponsor will be responsible for ensuring that the investigational product and placebo are manufactured in accordance with applicable current Good Manufacturing Practice (cGMP) regulations and requirements.

The investigational product and placebo will be labelled according to the requirements of local law and legislation.

BLU-5937 tablets or placebo will be provided for Period 1 and 2 by [redacted] in treatment kits containing 4 opaque HDPE bottles per kit for each period. Each bottle represents one of 4 dose levels (25, 50, 100, 200 mg BID). The investigational product will be administered as 25 mg tablets (for the 25, 50, 100 mg BID dose levels) or 200 mg tablets (for the 200 mg BID dose level) or matching placebos. BID dosing means every 12 hours, +/- approximately 1 hour. Each bottle will contain sufficient medication to cover the 4 -day treatment duration plus 1 extra day (total 5 days). When a new dose is dispensed it is to be started the following morning after the cough recording device is removed. There is no flexibility in visit window for Treatment visits; each dose is to be taken for 4 days.

Table 3. Treatment Kit Dispensing

Study DayNo.[#]	BLU-5937 Dose*/Placebo
Period 1 (treatment kit dispensing)	
Days 1-4	25 mg (1 tablet) BID or placebo
Days 5-8	50 mg (2 tablets) BID or placebo
Days 9-12	100 mg (4 tablets) BID or placebo
Days 13-16	200 mg (1 tablet) BID or placebo
Washout 10-14 days	
Day 17-30	No treatment
Period 2 (treatment kit dispensing)	
Days 31-34	25 mg (1 tablet) BID or placebo
Days 35-38	50 mg (2 tablets) BID or placebo
Days 39-42	100 mg (4 tablets) BID or placebo
Days 43-46	200 mg (1 tablet) BID or placebo

*Product can be administered without regard to meals

[#]*Day No. in the table assumes a 14-day washout period*

Once it is confirmed the subject has provided written consent and meets all the inclusion and none of the exclusion criteria the investigational product and placebo will be dispensed to individual subjects as per the randomization schedule.

Further details regarding packaging, labelling and accountability can be found in the pharmacy manual.

5.2.2. Storage and Handling

Investigational product will be shipped from [redacted] storage directly to site as subject screening commences. Additional kits will be sent once patients are randomized.

[redacted]

Each site will maintain an inventory record of the investigational product and placebo kits received, stored (in a secure restricted area), and dispensed per the randomization schedule and per treatment period.

The investigational product and placebo will be provided to study subjects only.

5.2.3. Method of Assigning Subjects to Treatment Groups

Subjects who have met all the inclusion/exclusion criteria and have read, understood and signed the informed consent form will be randomized 1:1 to treatment sequence (placebo then study drug or study

drug then placebo). The randomization will be produced by [redacted] The treatment will be allocated via a web-based electronic data capture system.

5.2.4. Blinding

This study is double-blind. Treatment assignments will be blinded to the investigator, subjects and all clinical and research staff for the entire study. [redacted] supplied and managed by [redacted] is the randomization system in use for this study. Blinded kit allocation to eligible subjects is managed by site staff via [redacted] (randomization & Resupply).

The study blind will be broken upon completion of the clinical study and after the study database has been locked.

During the study, the randomization code must not be broken except in emergency situations where the identification of a subject's study treatment is required by the qualified investigator for further treatment to the subject or to complete a serious adverse event (SAE) report. The qualified investigator (PI or delegated Sub-Investigator) will unblind the subject via the [redacted]. In case of emergency & neither the PI & Sub-Investigator are available, the Medical Monitor can as last resort conduct the unblinding through the [redacted] . The date and reason for breaking the blind will be recorded, and Sponsor & Medical Monitor will be notified. This information is to be stored in the subject's source files with as few of the site staff unblinded as is clinically reasonable.

5.2.5. Study Drug Accountability

Complete and accurate inventory records of all study drugs will be kept. This includes acknowledgment of receipt of each shipment of study product (kit quantity and condition), subject dispensing records, and returned or lost study product. Drug accountability will be performed at the end of each dose level.

All unused investigational products and all medication containers will be returned to the Sponsor.

5.2.6. Treatment compliance

The prescribed dosage, timing and mode of administration for study medication should not be changed from the protocol schedule. Departures from the intended regimen will be reported as protocol non-compliance. At each visit when a dose is ending, prior to dispensing study medication, previously dispensed study medication will be retrieved by the Investigator or designee and compliance assessed. Subjects exhibiting poor compliance, as assessed by tablets counts, should be counselled on the importance of good compliance with the study dosing regimen.

However, in exceptional circumstances and in discussion with medical monitor a subject may defer a visit by 1 day while continuing study medication.

Noncompliance is defined as taking more or less than 100% of prescribed study medication during any evaluation period (visit to visit).

6. STUDY PROCEDURES

Unless otherwise stated in this protocol, the standard operating procedures (SOPs) of the sites, will be followed during this study.

Any deviation from protocol procedures should be noted in the Case Report Forms (CRFs)/source documents. Protocol waivers and exemptions will not be authorised.

An overview of the study activities is detailed in the Schedule of Activities (Table 1) located after the Synopsis.

6.1. Safety Assessments

Safety assessments will include physical examination, vital signs, 12-lead ECG, clinical laboratory tests, and AE/concomitant medication monitoring. Additional safety measurements may be performed at the discretion of the investigator for reasons related to subject safety.

6.1.1. Medical History

The medical history at screening will include all queries by the medical and clinical staff related to the subject's well-being and history of relevant past medical events/experiences. Medical history will include all demographic data (year of birth, gender, race, body weight, height, and BMI). Alcohol and any smoking history will also be recorded.

6.1.2. Physical Examination

A complete physical examination will be performed by a medically qualified and licensed individual as scheduled in Table 1 (Schedule of Activities) at screening and end of study or early termination. The physical examination will include a general review of the following body systems (at minimum): head and neck, cardiovascular, respiratory, abdomen, brief neurological and general appearance. A brief physical examination (general appearance, lungs, heart, abdomen) evaluation will be performed at other site visits.

6.1.3. Vital Signs

Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature) will be measured as specified in Table 1 (Schedule of Activities). The subject's height and weight will be measured at Screening. Body mass index (BMI) will be calculated.

6.1.4. 12-Lead Electrocardiogram

A twelve-lead ECG will be performed at screening. ECG measurements will be taken during the study periods as specified in Table 1 (Schedule of Activities).

6.1.5. Laboratory Evaluations

Samples for Biochemistry, Haematology, Urinalysis, Urine Drug screen, and pregnancy testing (when necessary) will be collected as outlined in Table 1 (Schedule of Activities) and analysed at a central laboratory unless otherwise specified. Detailed instruction regarding sample collection, processing, and shipments may be found in the Laboratory Manual.

Laboratory assessments will include the following:

Table 4 Clinical Laboratory Evaluations

Clinical Laboratory Test Panel	Description	Visits
General biochemistry:	Sodium, potassium, chloride, glucose, blood urea nitrogen (BUN), creatinine, albumin, amylase, uric acid, creatinine kinase (CK), calcium, chloride, magnesium, glucose, potassium, sodium, bicarbonate. Lipids: TC, HDL-C, LDL-C, and TGs	Screening, Day 1, 16, 31, 46. Day 1, 16, 31, 46.

	LFT panel: (bilirubin total, bilirubin direct and indirect, ALP, AST, ALT, GGT)	Screening, Day 1, 4, 8, 12, 16, 31, 34, 38, 42, 46
Haematology:	White cell count with differential (absolute values of neutrophil, lymphocyte, monocyte, eosinophil, and basophil), red cell count, hemoglobin, hematocrit, mean corpuscular volume (MCV), MCH, MCHC, RDW and platelet count	Screening, Day 1, 16, 31, 46.
Coagulation	PT, INR, aPTT	Screening, Day 1, 4, 8, 12, 16, 31, 34, 38, 42, 46
[redacted]	[redacted]	[redacted]
Urinalysis:*	Color, clarity, specific gravity, pH, leukocyte esterase, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen. *Urine Microscopy will be performed if blood, protein, leukocyte esterase, and/or urobilinogen is abnormal	Screening, Day 1, 16, 31, 46
Urine drug screen:	Amphetamines, barbiturates, cannabinoids, cocaine, opiates and phencyclidine	Screening, Day 1, 16, 31, 46
Serum Pregnancy test:	To be performed for female subjects of childbearing potential	Screening
Urine Pregnancy test:	To be performed for female subjects of childbearing potential	Day 1, 16, 31, 46

The Principal Investigator or delegate will assess each abnormal value to determine if it is clinically significant. Post first dose clinically significant laboratory values will be reported as AEs. Only test results required by the protocol and/or abnormal results will be entered in the clinical database and reported in the Clinical Study Report, based on report requirement.

[redacted]

6.2. Blood Volume Collected

Blood samples will also be collected for PK assessments. The total volume of blood withdrawn, including volume required for screening, on-study and poststudy tests, should be approximately 250 mL per subject. The total blood taken may be higher if repeat blood samples are required for safety assessments.

6.3. Pharmacokinetic Assessments

The complete PK blood sampling schedule is presented in Table 1 (Schedule of Activities). The date and time of morning dosing PK sample collection and the date and time of the post dose PK samples will be recorded in the CRF/source documents.

Detailed instruction regarding PK sample collection, processing, and shipments may be found in the Laboratory Manual.

[redacted]

6.5. Efficacy Parameters

The anti-tussive effect of BLU-5937 will be assessed using the following tools at the time points specified in Table 1 (Schedule of Activities).

- ***Objective Cough Frequency*:** Objective cough frequency will be measured as 24-hour sound recordings using a custom-built digital recording device (VitaloJAK, Vitalograph, Ltd).
- ***Cough Severity Visual Analogue Scale (VAS)*:** Scored on a 100 mm visual analogue scale. At screening to be representative of the previous 2 weeks. At subsequent visits VAS rating refers to cough severity over previous 24 hours.
- ***Leicester Cough Questionnaire (LCQ):*** The LCQ is a cough specific quality of life assessment.
- ***Global Rating of Change Scale:*** An instrument used by subjects to assess any change in cough frequency since commencing study medication. It consists of 4 questions (see APPENDIX 3)

6.6. Study Visits

6.6.1. Screening Period Procedures (Visit 1/Day -14 to Day -1) in Clinic

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates and written informed consent obtained. Once informed consent has been obtained, the following procedures and evaluations will be performed:

- Assessment of inclusion and exclusion criteria
- Cough severity VAS, **for cough severity over the past 2 weeks**
- Medical history (including history of any medications within 30 days prior to Screening and chronic cough treatments within 1 year prior to Screening and history of tobacco and alcohol use) and demographics (including year of birth, sex, race, and ethnicity)
- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, body temperature)
- Weight, height & BMI (latter to be calculated automatically in the eCRF)
- Complete physical examination
- Spirometry
- Review of Chest radiograph or CT Thorax from within the past 12 months

- ECG (12 lead)
- Record all concomitant medication use
- Urine and blood for clinical laboratory tests, coagulation, LFTs, lipids, urine drug screen and urinalysis, including serum pregnancy test for women of childbearing potential
- Instruct subject in the use of the cough monitor, and arrangements for its collection
- Attach and activate the Screening (Day -14 to Day -1) cough monitor (preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose.

The Screening Period may be extended (beyond 14 days) by the Medical Monitor if additional information is required to ensure subject safety.

6.6.2. Randomization (Day -4 to Day 1)

Initial shipment of IP to a site is triggered (in [redacted] by PM or delegate) once their first subject has started screening. During the screening period the subject will be assessed for eligibility for the trial. Once it is confirmed the subject is eligible (between days -4 and Day 1) the subject will be randomized (triggering additional shipment to the site of investigational drug kits for further treatment period/randomizations).

6.6.3. Baseline Visit Procedures Period 1 (Visit 2/Day 0) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Attach and activate the Baseline cough monitor (preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose.
- Record any Adverse Events (AEs) since Consent was confirmed, or add to Medical History
- Record any change in concomitant medication use
- Perform cough severity VAS, for cough severity over the past 24 hours
- Schedule Visit 3/Day 1 at clinic

6.6.4. Treatment Visit Procedures (Visit 3/Day 1)

The following procedures and evaluations will be performed:

- Confirm inclusion and exclusion criteria
- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature) pre-dose
- ECG (12 lead) pre-dose and [redacted]
- Urine and blood for clinical laboratory tests [redacted] coagulation, LFTs, lipids, urine drug screen and urinalysis, including urine pregnancy test for women of childbearing potential (pre-dose)
- Brief physical examination (pre-dose)
- The following will be completed by the subject (pre-dose):
  - LCQ

- Collect the Baseline cough monitor (pre-dose)
- Blood PK samples (pre-dose [redacted])
- If not already done (Days -4 to Day 0) randomize the patient to a study treatment using the [redacted] randomization Module
- Record kit number and dispense allocated study treatment
- Study drug
    - Dispense Visit 3 drug (Days 1-4 bottle)
    - Observe AM dose of study drug (before 10am)
- Record all AEs
- [redacted]
- Record any change in concomitant medication use
- Schedule Visit 4/Day 4 at clinic or with home health nurse (as applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.5. Treatment Visit Procedures (Visit 4/Day 4) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Blood for LFTs and coagulation (pre-dose)
- Blood PK samples (pre-dose [redacted])
- Attach and activate the Visit 4/Day 4 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject (pre-dose):
    - Cough severity VAS for cough severity over the past 24 hours
    - Global Rating of Change Scale
- Study drug
    - Observe AM dose of study drug (before 10am)
    - Dispense Visit 4 drug (Days 5-8 bottle)
- Record all AEs
- [redacted]
- Record any change in concomitant medication use

- Confirm arrangements for collection of the cough monitor
- Schedule Visit 5/Day 8 Visit at clinic or with the mobile research nurse (if applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.6. Treatment Visit Procedures (Visit 5/Day 8) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Blood for LFTs and coagulation (pre-dose)
- Blood PK samples (pre-dose [redacted]
- Attach and activate Visit 5/Day 8 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
- Study drug
  - Observe AM dose of study drug (before 10am)
  - Dispense Visit 5 drug (Days 9-12) bottle
- Record all AEs
- [redacted]
- Record any change in concomitant medication use
- Confirm arrangements for collection of the cough monitor
- Schedule Visit 6/Day 12 at clinic or with home health nurse (if applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.7. Treatment Visit Procedures (Visit 6/Day 12) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Blood for LFTs and coagulation (pre-dose)

- Blood PK samples (pre-dose [redacted])
- Attach and activate Visit 6/ Day 12 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
- Study drug
  - Observe AM dose of study drug (before 10am)
  - Dispense Visit 6 drug (Days 13-16) bottle
- Record all AEs
- [redacted]
- Record any change in concomitant medication use
- Schedule Visit 7/Day 16 at clinic

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.8. Treatment Visit Procedures (Visit 7/Day 16) in clinic

The following procedures and evaluations will be performed:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Urine and blood for clinical laboratory tests, coagulation, LFTs, lipids, urine drug screen and urinalysis, including urine pregnancy test for women of childbearing potential (pre-dose)
- Blood PK samples (pre-dose and 1-hour post dose)
- Complete physical examination
- Attach and activate Visit 7/Day 16 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
  - LCQ
- Study drug
  - Observe AM dose of study drug (before 10am)
  - Perform accountability for Visits 3-7 (Days 1-16 bottles)

- Record all AEs
- [redacted]
- Record any change in concomitant medication use
- Schedule Visit 8/Day 30* at clinic or with home health nurse (if applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

***The Washout Period may be extended (beyond 14 days) by the Medical Monitor if additional information is required or to aid scheduling.**

6.6.9. Washout Period (Days 17-30)

Washout period may be 10 - 14 days to allow for flexible scheduling. **The Washout Period may be extended (beyond 14 days) by the Medical Monitor if additional information is required or to aid scheduling.**

6.6.10. Baseline Visit Procedures Period 2 (Visit 8/Day 30) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Attach and activate the Visit 8 cough monitor (preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject:
  - Cough severity VAS for cough severity over the past 24 hours
- Record any change in concomitant medication use
- Record all AEs
- [redacted]
- Schedule Visit 9/Day 31 visit at the clinic

6.6.11. Treatment Visit Procedures (Visit 9/Day 31) in clinic

The following procedures and evaluations will be performed:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Collect the baseline cough monitor (pre-dose)
- Urine and blood for clinical laboratory tests (including biomarker ATP sample for sub-study), coagulation, LFTs, lipids, urine drug screen and urinalysis, including urine pregnancy test for women of childbearing potential (pre-dose)
- Blood PK samples (pre-dose [redacted])

- Brief physical examination
- The following will be completed by the subject (pre-dose):
  - LCQ
- Allocate (blinded) Treatment Period 2 kit using [redacted]

Record kit number and dispense allocated study treatment

- Study drug
  - Observe AM dose of study drug (before 10am)
  - Dispense Visit 9 drug (Days 31-34) bottle
- Record all AEs
- [redacted]
- Record any change in concomitant medication use
- Schedule Visit 10/Day 34 at clinic or with home health nurse (if applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.12. Treatment Visit Procedures (Visit 10/Day 34) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Blood for LFTs and coagulation (pre-dose)
- Blood PK samples (pre-dose [redacted])
- Attach and activate the Visit 10 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
- Study drug
  - Observe AM dose of study drug (before 10am)
- Dispense Visit 10 drug (Days 35-38) bottle
- Record all AEs
- [redacted]

- Record all concomitant medication use
- Confirm arrangements for collection of the cough monitor
- Schedule Visit 11/Day 38 Visit at clinic or with home health nurse (if applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.13. Treatment Visit Procedures (Visit 11/Day 38) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Blood for LFTs and coagulation (pre-dose)
- Blood PK samples (pre-dose and [redacted]
- Attach and activate Visit 11cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
- Study drug
  - Observe AM dose of study drug (before 10am)
- Dispense Visit 11 drug (Days 39-42) bottle
- Record all AEs
- [redacted]
- Record all concomitant medication use
- Confirm arrangements for collection of the cough monitor
- Schedule Visit 12/Day 42 Visit at clinic or with home health nurse (if applicable)

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.14. Treatment Visit Procedures (Visit 12/Day 42) in clinic or at home

The following procedures and evaluations may be performed at the clinic or at the subject's home by the home health nurse:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- ECG (12 lead) pre-dose and 1-hour post dose
- Blood for LFTs and coagulation (pre-dose)

- Blood PK samples (pre-dose [redacted])
- Attach and activate Visit 12 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later, prior to the start of the new dose
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
- Study drug
  - Observe AM dose of study drug (before 10am)
  - Dispense Visit 12 drug (Days 43-46) bottle
- Record all AEs
- [redacted]
- Record any changes in concomitant medication use
- Confirm arrangements for collection of the cough monitor
- Schedule Visit 13/Day 46 Visit at clinic

Subjects will be instructed to immediately contact the study centre if they experience intolerable AEs at any time during the treatment period.

6.6.15. Treatment Visit Procedures (Visit 13/Day 46/Early Termination Visit) in clinic

The following procedures and evaluations will be performed at the clinic on Day 46 or at Early Termination:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- Complete physical exam
- ECG (12 lead) pre-dose and 1-hour post dose
- Urine and blood for clinical laboratory tests, coagulation, LFTs, lipids, urine drug screen and urinalysis, including urine pregnancy test for women of childbearing potential (pre-dose)
- Blood PK samples (pre-dose [redacted])
- Attach and activate Visit 13 cough monitor (pre-dose, preferably before 10am). Cough Monitor is to be removed 24 hours later
- The following will be completed by the subject (pre-dose):
  - Cough severity VAS for cough severity over the past 24 hours
  - Global Rating of Change Scale
  - LCQ
- Study drug

- Observe AM dose of study drug (before 10am)
- Perform accountability for Visits 9-13 (Days 31-46 bottles)

- Record all AEs
- [redacted]
- Record any change in concomitant medication use
- Confirm arrangements for collection of the cough monitor
- Schedule Visit 14/Day 60 visit at clinic

6.6.16. Follow-Up Visit Procedures (Visit 14/Day 60) in clinic

Subjects will return to the clinic 14 days after Visit 13/Day 46/Early Withdrawal, for the following procedures and evaluations:

- Vital signs (sitting systolic and diastolic blood pressure, pulse, respiration, temperature)
- Brief physical examination
- Attach and activate Visit 14 cough monitor (preferably before 10am). Cough Monitor is to be removed 24 hours later
- The following will be completed by the subject:
  - Cough severity VAS for cough severity over the past 24 hours
  - Global rating of change scale
- Record all AEs
- [redacted]
- Record all concomitant medication use
- Confirm arrangements for collection of the cough monitor

6.6.17. Early Termination

Early termination from the study may occur due to loss to follow-up or withdrawal of consent by the subject. In accordance with legal requirements and ICH GCP, every subject or his/her legal representative has the right to withdraw from the study at any time and without providing reasons. If a subject is willing to provide a reason for withdrawal, this will be recorded in the CRF/source documents (see also 4.3.3 Individual Subject Stopping Rules; 5.2.6 Treatment Compliance).

7. ADVERSE EVENTS DOCUMENTATION

7.1. Definitions

An AE is defined as any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavourable and unintended sign (including a clinically significant abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

An adverse reaction (AR) is any AE for which there is a reasonable possibility the drug caused the AE. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE Table 5. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE may be:

- A new illness,
- Worsening of a concomitant illness,
- An effect of the study medication including comparator; it could be an abnormal clinical laboratory value as well as a significant shift from baseline within normal range which the investigator considers to be clinically important.

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

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity (defined as a substantial disruption of a person's ability to conduct normal life functions),
- Is a congenital anomaly or birth defect,
- Is an important medical event that may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above (according to medical judgment of the investigator)

The following is not considered to be an SAE:

- Any elective procedures that require admission to hospital as well as any planned elective procedures (e.g., angioplasty) planned prior to signing a consent sent form are not considered SAEs (unless the underlying condition has worsened or the procedure results in a worsening of the subject's condition). This should be recorded in the medical history.
- A visit to an Emergency Room or other hospital department <24 hours that does not result in an admission to hospital (unless it is considered an important medical event or life threatening event) these should be recorded as an AE.

7.2. Severity Assessment

All AEs will be graded as mild, moderate, or severe according to the following definitions:

Mild: Causing no limitation of usual activities; the subject may experience transient slight discomfort

Moderate: Causing some limitation of usual activities; the subject may experience annoying discomfort

Severe: Causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain

Every effort will be made to obtain an adequate evaluation of the severity.

7.3. Causality Assessment

The qualified investigator will determine the relationship of any AE to the study drug using the guidelines presented in Table 5

Table 5. Adverse Event Relationship to Study Drug

Relationship to Drug	Comment
Definite	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically using a satisfactory re-challenge (the drug is re-administered to determine if the same reaction occurs) procedure if necessary.
Probable	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to the drug administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely ("Not related")	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide plausible explanations.
Not related	Any event that does not meet the above criteria; there is sufficient information that aetiology of the event is in no relation to the study drug.

7.4. Adverse Event Monitoring

For the purposes of this study, the monitoring period for AEs extends from the signature of informed consent (screening) until the follow-up visit.

From signature of informed consent (screening) to the first dose of the study, AEs will be recorded as screening events or as part of the medical history, as applicable.

AEs occurring after first dose of study medication will be indicated as treatment-emergent AEs (TEAEs) in the clinical study report.

Subjects will be questioned on their health status at each subject contact through to follow up visit. Open-ended questions will be asked.

During the study, all AEs spontaneously reported by the subject, observed by the clinical staff or elicited by general questioning will be recorded for all subjects and reported in the CRF/source documents.

[redacted]

If necessary, every effort will be made to obtain an adequate follow-up of the subjects. Should any subject choose to withdraw from the study, they will be advised of the safety precautions to be taken.

The Investigator must make every effort to follow-up any AE which remains unresolved as of the last visit regardless of attribution until judged resolved or a reasonable explanation for its persistence found or is deemed mild and safely resolving or the subject is lost to follow up.

In the case of AEs deemed related to the Investigational Product, every effort will be made to determine the final outcome.

Classification of AEs will be performed by System Organ Class (SOC) and Preferred Term (PT) using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

Concomitant medications will be coded using the most recent version of the World Health Organization drug dictionary.

7.5. Reporting of Pregnancy

Pregnancy in a female study subject shall be reported to the sponsor on the provided pregnancy reporting form within 24 hours of the knowledge of its occurrence by the qualified investigator or delegate (for pregnancies occurring during the course of the study or within 4 weeks after the last drug administration). Because of the possibility the foetus/embryo could have been exposed to the study drug through the parent and for the subject's safety, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications.

Pregnancy that occurs within 4 weeks after the last drug administration in a female partner of a male study subject shall be reported to the sponsor within 24 hours of the knowledge of its occurrence by the clinical site that such pregnancy occurred during the course of the study or right after. Because of the possibility that the foetus/embryo could have been exposed to the study drug through the parent and for the safety of the subject's female partner, the pregnancy will be followed up to determine its outcome, including spontaneous or voluntary termination, details of birth, presence or absence of any birth defects, congenital anomalies, or maternal and/or newborn complications and will be reported as an SAE.

The pregnancy will be recorded and reported by the clinical site to the sponsor. Pregnancy follow-up will also be properly recorded to ensure quality and completeness of the data belonging to the study drug and will include an assessment of the possible causal relation between the study drug and any pregnancy outcome. Any SAE experienced during pregnancy will be reported on an SAE Report Form.

Please see the Pregnancy Reporting Form Completion Guidelines for safety reporting instructions as per Diamond PV Safety Plan.

7.6. Serious Adverse Event Reporting

The site will notify any SAE to the sponsor, pharmacovigilance, Medical Monitor, Regulatory team and Illingworth, within 24 hours after becoming aware of its occurrence (as per Diamond PV Safety Plan).

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The initial SAE report must be as complete as possible, including details of the current illness and SAE, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g. an end date for the AE, laboratory values received after the report, or hospital discharge summary) must be documented. All follow-up information must be reported as soon as the relevant info is available.

The notification should be directed to:

[redacted]

The expectedness of an SAE shall be determined by the Sponsor according to the most recent version of the investigator's brochure. An SAE will be considered "unexpected" if the AE is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected," as used in this definition, also refers to AEs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Please see the SAE Form Completion Guidelines for safety reporting instructions as per [redacted] Safety Plan.

7.7. Serious Adverse Event Reporting to Regulatory Authorities and study Investigators

Any new and unexpected AEs may be reported to the IRB or IEC as required by local Regulations.

Suspected unexpected serious adverse reactions (SUSARs) are AEs that are believed to be related to study drug and are both unexpected (i.e., the nature or severity is not expected from the information provided in the Investigator Brochure) and serious. SUSARs are subject to expedited reporting to the Regulatory Authorities and IRB & EC as appropriate.

Investigators will be notified by the Diamond PV Limited of all SAEs that require prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor or CRO. The Sponsor or CRO will ensure that the appropriate regulatory authorities are notified of all reportable SAEs.

8. DATA ANALYSIS AND STATISTICAL METHODS

8.1. Analysis Sets

Inclusion of subjects in the various analysis sets will be determined and documented prior to study unblinding.

The **Screen Set** will include all subjects who signed the informed consent.

The **Enrolled Set** will include all subjects who passed screening irrespective of whether they received study treatment.

The **Randomized Set** will include all subjects assigned a randomization number, irrespective of whether they go on to receive treatment. If this analysis set coincides with the intention-to-treat analysis set, it will be omitted.

The **Intention-to-treat (ITT) Set** will include all randomized subjects who take at least one dose of study medication and provide at least one baseline and at least one post-baseline cough frequency measurement. Analyses will be conducted by planned treatment. This analysis set will be the primary efficacy analysis set.

The **Per-Protocol (PP) Set** will be a subset of the ITT set who do not violate inclusion or exclusion criteria and/or deviate from the protocol, in a way that could influence their efficacy assessment. Consequently this analysis set will be used for sensitivity analyses of efficacy endpoints. Given the crossover design the inclusion in this set will consider each study period separately (i.e. a subject could be included in this set for one period but excluded from the other).

The **Safety Analysis (SAF) Set** will include all subjects who receive at least one dose of either BLU-5937 or placebo. Analyses will be conducted by treatment received.

The **Pharmacokinetic Set** will include all subjects in the SAF set who have at least one evaluable (i.e. not impacted by any important protocol deviations or other events) post-dose PK measurement (even if below the limit of quantification). Subjects will be analyzed according to the treatment received and dose taken.

8.2. General Approach

Full details of all planned analyses shall be specified in the SAP which will be finalized prior to database lock.

For continuous variables, the number of observations, mean, standard deviation, median, minimum and maximum shall be presented as appropriate. For categorical values, the number of observations and percentages shall be presented as appropriate.

Subject-level listings shall be provided to support all tabulated output.

8.3. Demographic Data and Other Baseline Characteristics

Disposition, demographic data (e.g. age, gender and race) and other baseline characteristics including medical and medication history shall be summarized.

8.4. Efficacy Analysis

8.4.1. Primary Endpoint – Awake Cough Count

The primary efficacy endpoint is change from baseline in awake cough count by dose level derived as follows:

$$\text{Change in Awake Cough Count} = \text{Post-treatment Cough Count} - \text{Baseline Cough Count}$$

Hence a negative result indicates a decrease in cough frequency while a positive result indicates an increase.

Due to the skewed nature of cough frequency data, awake cough frequency will be log transformed prior to analysis.

The baseline scores will be recorded on Day 0 (Visit 2) and Day 30 (Visit 8) for Periods 1 and 2 respectively.

If there are any zero cough frequencies within the data all values will have 0.1 added to their cough frequency (equates to 1 cough every 10 hours) prior to transforming the data.

A repeated measures mixed model analysis of variance will be used to evaluate the primary endpoint. The log transformed awake cough frequency measured at assessment visits within periods will be the repeated measure.

A repeated measure mixed model (MMRM) suitable for a crossover design with repeated measures within periods will be used. The fixed effects, random effects and repeated measure structure for the model will be as follows:

Fixed effects: Sequence (AB, BA), Period (1, 2), Treatment (BLU-5937, Placebo), Assessment Visit (1 to 4 within each period) and the Treatment by Assessment Visit interaction. Average baseline (average of the 2 period baselines) and period specific baselines will be included as covariates.

Random Effects: Subject

Repeated measures structure: the model will take account of the assessment visits within subject periods

Contrast statements will be used to compare each dose of active treatment against placebo at the corresponding assessment visits of the periods. The mean change from baseline (on the log scale), with associated standard errors will be presented for each treatment at each assessment visit. Treatment differences vs placebo with corresponding 95% CIs will also be presented for each dose. Means will be back-transformed to estimate the ratio of the visit to baseline for each treatment at each visit and the treatment differences will be back-transformed to estimate the ratio of the visit to baseline for the active group, adjusted for the placebo effect. All ratios will be accompanied by their 95% CIs and the p-values comparing active doses to placebo will be presented.

Geometric mean profile plots against day will be produced with asymmetric error bars (back-transformed from the log scale), with separate lines for each treatment.

The percent difference change between BLU-5937 doses and placebo will be estimated by 100 * e(diff - 1); where diff is the difference provided by the analysis of the log-transformed variable.

Using an MMRM analysis is suitable when assuming missing data is missing at random (MAR).

Alternative sensitivity analyses will be performed:

- the reasons for data being missing will be reviewed prior to unblinding the randomization. If the reason for missingness is deemed as being potentially related to lack of treatment response, the missing value will be imputed with the worst cough score (for that patient) recorded. If the subject withdraws prior to Period 2 their missing Period 2 data will not be imputed in this way. After imputation scores will be analysed using the methods described for the primary analysis.
- the primary analysis will be repeated using the PP analysis set.
- the primary analysis assumes that the data are log-normally distributed. An analysis will also be performed of the untransformed data. On this scale changes from baseline and differences with placebo for the changes from baseline will be estimated along with 95% confidence intervals.

8.4.2. Secondary Endpoints

The following secondary endpoints will be analysed using the ITT analysis set.

- Change from baseline in 24-hour cough frequency at end of each dose level and follow-up
- Change from baseline in awake cough frequency at follow up

- Change from baseline in cough severity as measured by the Visual Analogue Scale (VAS) at end of each dose level and follow-up
- Change from baseline in Leicester cough questionnaire (LCQ) total scores at end of each treatment period
- Global rating of change scale at end of each dose level and follow-up

Statistical approaches for analysis of the secondary endpoints will be detailed in the SAP and will be generally similar in approach to that of the primary endpoint. Only cough count data will be log transformed prior to analysis.

Global rating of change scale will be remapped and given scores to create a continuous endpoint. A lower score will be considered a more positive outcome.

8.4.3. Exploratory Efficacy Endpoints

The analyses of exploratory endpoints will be described in the statistical analysis plan.

Cough data will be log transformed prior to analysis and appropriately back transformed for presentation of results.

8.5. Multiplicity

No adjustment for multiplicity is required.

8.6. Extent of Exposure

Exposure data will be summarized by treatment group.

8.7. Safety Analysis

Adverse events will be classified into standardized medical terminology from the verbatim description (Investigator term) using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be presented by preferred term nested within System Organ Class. Verbatim description and all MedDRA level terms, including the lower level terms, for all AEs will be contained in the data listings of the CSR.

Adverse events will be summarized by presenting, for each treatment group, the incidence of AEs. Although a MedDRA term may be reported more than once for a subject, that subject will be counted only one time in the incidence count for that MedDRA term. In addition to presenting summaries by treatment group, AEs emergent from Days 1-4, Days 4-8, Days 8-12 and Days 12-16 will also be presented, with the break points being the start of dosing for each dose phase.

Only treatment-emergent adverse events (TEAEs) will be summarized. Adverse events that are not treatment-emergent will be listed. Treatment-emergent adverse events are defined as AEs that

- emerge during treatment, having been absent at pre-treatment (Baseline) or:
- re-emerge during treatment, having been present at Baseline but stopped prior to treatment, or
- worsen in severity during treatment relative to the pre-treatment state, when the AE is continuous

Taste disturbance AE's will also be presented and summarized.

8.8. Laboratory Values

Clinical laboratory results post-Baseline will be evaluated for markedly abnormal values.

Parameters and their changes from baseline will be summarized by treatment group and visit. Shift from baseline tables will also be presented by treatment group and visit.

8.9. Vital Signs

Vital sign values will be evaluated on an individual basis and abnormal values will be identified as those outside (above or below) the reference range. Parameters and their changes from baseline will be summarized by treatment group and visit.

8.10. ECG

Parameters and their changes from baseline will be summarized by treatment group and visit. QTcF values will be summarized categorically by treatment group (e.g. increase in QTcF ≥60 msec from baseline and absolute QTcF value of ≥500 msec).

8.11. PK Analysis

Plasma concentrations of BLU-5937 will be presented graphically (individual and median plots) and summarised by day and nominal timepoint.

8.12. PK/PD Relationship

The relationship between systemic concentrations of BLU-5937 and the following will be explored graphically:

- reductions in awake cough frequency
- taste disturbance AEs

[redacted]

8.13. Planned Interim Analyses

No formal interim analyses will be performed; blinded safety, tolerability and available PK data will be reviewed by the SRC following completion of each cohort dosed.

8.14. Determination of Sample Size

[redacted]

9. ETHICS

9.1. Independent Ethics Committee / Institutional Review Board

This protocol and the ICF will be submitted to an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to initiation of the study, and the study will not start until the Board has approved the documents. Notification of the Board's approval will be appended to the final report.

9.2. Ethical Conduct of the Study

This study will be conducted in compliance with the study protocol, the ethical principles that have their origins in the Declaration of Helsinki, the International Council on Harmonisation (ICH) Guideline E6 for Good Clinical Practice (GCP), the FDA GCP Code of Federal Regulations (CFR) Title 21 (part 56), the European regulation EU 536/2014, and the Tri-Council Policy Statement (Canada).

9.3. Subject Information and Consent

Before screening activities commence, each patient will be given a copy of the approved (IEC/IRB approval) PIL/ICF to read, this will provide a full explanation of the purpose of the study, the procedures to be carried out, and the potential risks of the study participation, in non-technical terms. Once this essential information is provided to the patient and the Investigator or delegate has the conviction the patient understands the implications of participating in the study, if the patient chooses to continue the screening process, they will be asked to sign and date a properly executed ICF prior to screening. Subjects will be assured they may withdraw from the study at any time without jeopardizing their medical care or future study participation (for which they qualify) related to or required as a result of study participation.

The original signed ICF will be maintained in the investigator site file, Subjects will be given a signed copy of the ICF.

If an amended or revised ICF is approved during the study, each subject will be re-consented at the next site visit.

9.4. Subject Confidentiality

The investigators and the sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. Subjects are provided with a unique subject identifier via the Syne-Clin randomization system, this will be used on all documents to identify the subjects. No subject identifiable data will be provided to the sponsor.

In compliance with local regulations/ICH GCP Guidelines, it is required the investigator and institution permit authorised representatives of the company, of the regulatory agency(ies), and IRB access to review the subject's original medical records for verification of study-related procedures and data.

The handling, processing and storage of laboratory samples will be described in the laboratory manual. The anonymised samples will be retained while research on the study treatment continues but no longer than 3 months after the end of the study.

Explicit consent to obtain the data and to share the data will be obtained from each subject as part of the informed consent process, prior to performing any study procedures.

10. DATA COLLECTION, RETENTION, AND MONITORING

10.1. Case Report Forms

Data required by the protocol is captured on Source Documents, then transcribed into an electronic data capture software (Syne-clin) by sites. This will be completed by appropriately delegated and trained site personnel for each subject included in the study (i.e. screening failure subjects and those who received an IP treatment).

The study monitor will review all source data (via access to medical records, laboratory data and other source documents) to allow the required CRF entries to be verified as accurate.

The cleaned and locked data will be approved and electronically signed by the Principal Investigator (PI) or delegate. The PI will subsequently be provided with a copy of their site's anonymised eCRF data for archiving with their ISF at study close-out. The data will be output in a CRF format to be included with

the final report provided to the sponsor. The sponsor only has access to anonymised data, no personal identifiable data will be shared with the sponsor.

10.2. Data Management and Processing

Data management activities will be performed using the [redacted]

Data entered will be checked for accuracy through QC checks. When the database is declared to be complete and accurate, it will be locked.

10.3. Record Retention

All essential documents and records will be maintained by the clinical site in accordance with, and for the period specified in the applicable regulatory requirement(s) seen to be 25 years.

10.4. Monitoring of the Study

The sponsor or its delegated study monitors will be responsible for monitoring the conduct of the study. A separate Monitoring Plan will include details regarding responsibilities of the study monitors, investigator responsibilities in providing access to records and addressing issues identified, frequency and structure if monitoring visits and adherence to subject confidentiality as outlined in the ICF.

The clinical site will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

11. ADMINISTRATIVE PROCEDURES

11.1. Adherence to Protocol

Excluding an emergency situation in which proper treatment is required for the protection, safety and well-being of the study subjects, the study will be conducted as described in the approved protocol and performed according to ICH GCP, local Regulations and guidelines. Any deviation from the protocol will be recorded and explained. Subject-related Protocol Deviation (PDs) will be logged in the [redacted] by each site. Lists per site will be printed & signed by their Principal Investigator.

If amendments to the protocol and/or amendments or revisions to the ICF are required, the modifications will be documented and submitted to an IEC/IRB for approval.

11.2. Statement of Investigator

The form "Principal Investigator Undertaking" will be signed by the investigator responsible for the medical decisions per site and care provided to their subjects (being also referred to as the "qualified investigator") prior to the commencement of his responsibilities with respect to the clinical trial, as required by the Food and Drug Regulations. The undertaking form will be maintained with the trial records and will be made available upon request.

11.3. Delegation of Investigator Duties

The Principal Investigators will ensure all personnel involved in the trial are adequately qualified and informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The Principal Investigators will maintain a list of Sub-Investigator(s) and other appropriately-qualified persons to whom he/she delegates significant trial-related duties.

11.4. Clinical Trial Application

A Clinical Trial Application must be submitted to the MHRA and an IND to the FDA prior to the study, and a "No Objection Letter" must be obtained before any drug administration whenever relevant.

11.5. Exemption Application for Controlled Substances

This trial does not involve a controlled substance.

11.6. Disclosure & Confidentiality

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator(s), the investigator's staff will not be disclosed in whole or in part to others or used for any purpose other than reviewing or performing the study without the written consent of the Sponsor. No data collected as part of this study will be used in any written work, including publications (e.g. manuscripts, abstracts, oral/slide presentations, book chapters), without the written consent of Sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in the Confidentiality Agreement between the Sponsor and the investigator(s), and investigators sites.

12. REFERENCES

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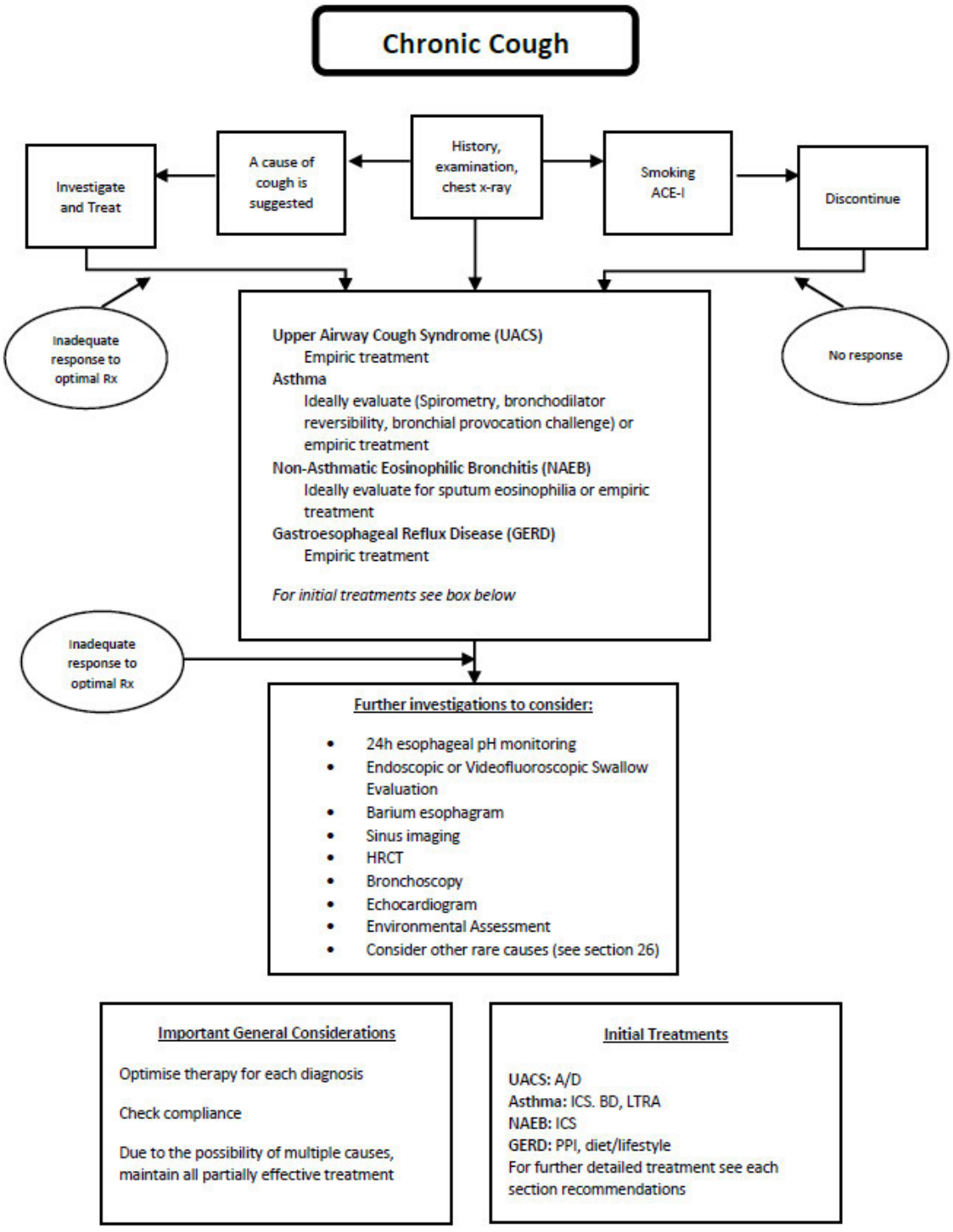
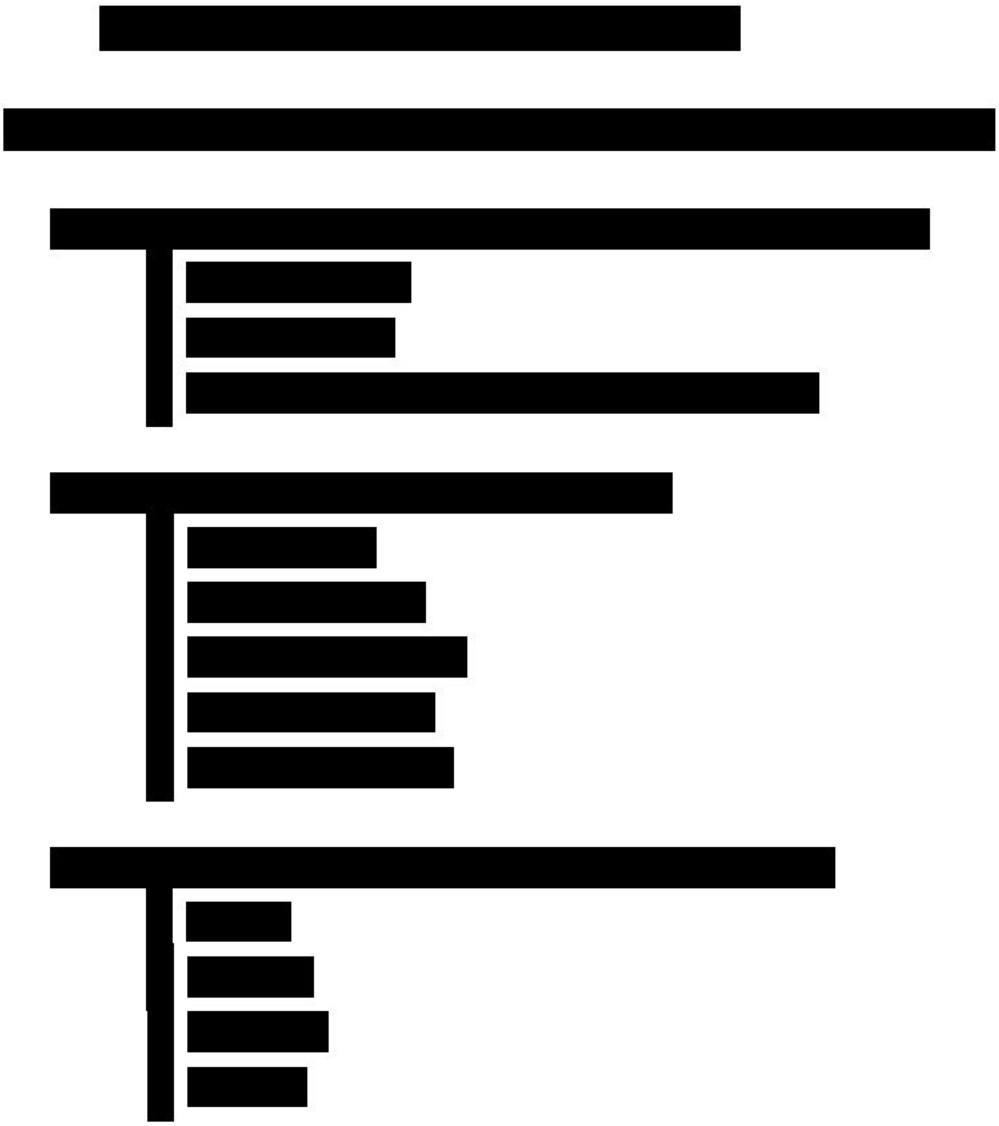
13. APPENDIX 1: ACCP/BTS Guidelines





15. APPENDIX 3: GLOBAL RATING of CHANGE SCALE

Overall, has there been any change in your <u>cough frequency</u> since you started the new medicine? Please indicate if there has been any change in your symptoms by choosing one of the following options. Are your symptoms:

□ WORSE

□ ABOUT THE SAME

□ BETTER

[Patients who state they are better are then asked:]

How much better are your symptoms? Are they:

1. ALMOST THE SAME, HARDLY ANY BETTER AT ALL
2. A LITTLE BETTER
3. SOMEWHAT BETTER
4. MODERATELY BETTER
5. A GOOD DEAL BETTER
6. A GREAT DEAL BETTER
7. A VERY GREAT DEAL BETTER

[Patients who state they are worse are then asked:]

How much worse are your symptoms? Are they:

8. ALMOST THE SAME, HARDLY ANY WORSE AT ALL
9. A LITTLE WORSE
10. SOMEWHAT WORSE
11. MODERATELY WORSE
12. A GOOD DEAL WORSE
13. A GREAT DEAL WORSE
14. A VERY GREAT DEAL WORSE

Overall, has there been any change in your <u>cough severity</u> since you started the new medicine? Please indicate if there has been any change in your symptoms by choosing one of the following options. Are your symptoms:

□ WORSE

□ ABOUT THE SAME

□ BETTER

[Patients who state they are better/worse are asked to clarify as below:]

[Patients who state they are better are then asked:]

How much better are your symptoms? Are they:

1. ALMOST THE SAME, HARDLY ANY BETTER AT ALL
2. A LITTLE BETTER
3. SOMEWHAT BETTER
4. MODERATELY BETTER
5. A GOOD DEAL BETTER
6. A GREAT DEAL BETTER
7. A VERY GREAT DEAL BETTER

[Patients who state they are worse are then asked:]

How much worse are your symptoms? Are they:

8. ALMOST THE SAME, HARDLY ANY WORSE AT ALL
9. A LITTLE WORSE
10. SOMEWHAT WORSE
11. MODERATELY WORSE
12. A GOOD DEAL WORSE
13. A GREAT DEAL WORSE
14. A VERY GREAT DEAL WORSE