A Phase 3, 52-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm Efficacy and Safety Study with Open-Label Extension of BLU-5937 in Adult Participants with Refractory Chronic Cough, Including Unexplained Chronic Cough (CALM-1)

Published: 05-12-2022
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This study has been transitioned to CTIS with ID 2024-513460-26-00 check the CTIS register for the current data. To assess the effect of BLU-5937 vs placebo on 24-hour cough frequencyin adults with RCC (including unexplained chronic cough) and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Upper respiratory tract disorders (excl infections)
Study type	Interventional

Summary

ID

NL-OMON56306

Source
ToetsingOnline

Brief title
BUS-P3-01 (CALM-1)

Condition

- Upper respiratory tract disorders (excl infections)

Synonym
Chronic Cough, RCC

Research involving
Human

Sponsors and support

Primary sponsor: Bellus Health, Inc.
Source(s) of monetary or material Support: The pharmaceutical industry

Intervention

Keyword: BLU-5937, Refractory Chronic Cough, Unexplained Chronic Cough

Outcome measures

Primary outcome

24-hour cough frequency at Week 12 by a cough monitor.

• Incidence of AEs and SAEs up to Week 52

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• Occurrences of study treatment discontinuations due to AEs and SAEs

up to Week 52

• Occurrences of AEs and SAEs leading to study withdrawal up to Week

52

• Changes from Baseline in vital signs (systolic and diastolic blood

pressure, heart rate, respiratory rate, body temperature, weight) at

Week 52

• Changes from Baseline in clinical laboratory values, (including male

reproductive hormones, hematological and clinical chemistry

parameters) at

Week 52

• Changes from Baseline in ECG values at Week 52

Secondary outcome

CS-VAS

• Change from Baseline in CS-VAS at Week 12

• CS-VAS response (achieving >= 30 mm reduction from Baseline in CSVAS score) at

Week

12

Objective cough frequency recording

• Awake cough frequency at Week 12

• 24-hour cough response (achieving 30% reduction from Baseline) at

Week 12

LCQ

• Change from Baseline in the LCQ total score at Week 12

• LCQ response (achieving >= 1.3-point increase from Baseline in total

score) at Week 12

CCD

• Change from Baseline in CCD score(24-hour symptom scale) at Week

12

• CCD response (achieving >=MCID improvement from Baseline, 24-hour

symptom scale)at Week 12

Study description

Background summary

Chronic cough is categorized as a cough lasting 8 weeks or more. Patients with chronic cough are evaluated and treated for potential underlying causes before

being designated as refractory. RCC is defined as chronic cough after the patient is treated for an identified underlying medical condition, as well as chronic cough for which an underlying medical condition has not been identified despite appropriate patient evaluation. It is thought that RCC is at least partially mediated by activation of P2X3 homotrimeric receptors on vagal C-fibers innervating the airways. P2X3 receptors are adenosine triphosphate (ATP) cation-gated channels located on primary afferent neurons in various tissues, including respiratory tract. ATP released from damaged or inflamed tissues acts on P2X3 receptors, triggering pain or irritation signals transmitted by sensory afferent fibers to the brain. Specifically, the P2X3 receptor appears to play a role in cough hypersensitivity and has been identified as an important target in RCC.
Although RCC is common, there are no medicines approved by the US Food and Drug Administration (FDA) nor by the European Medicines Agency (EMA) for the treatment of RCC. LYFNUA® (gefapixant Tablets 45 mg), another P2X3 antagonist, has been approved in Japan and Switzerland for the treatment of adults with refractory or unexplained chronic cough.
BLU-5937 is a small molecule, potent, selective, and non-competitive P2X3 homotrimeric receptor antagonist that is being developed as a potential treatment for RCC.

Study objective

This study has been transitioned to CTIS with ID 2024-513460-26-00 check the CTIS register for the current data.

To assess the effect of BLU-5937 vs placebo on 24-hour cough frequency in adults with RCC (including unexplained chronic cough) and Baseline 24-hour
cough frequency >=8 coughs/h at Week 12.
To determine the safety of BLU-5937 vs placebo in adults with RCC (including unexplained chronic cough) up to Week 52.

Study design

Double-blind treatment preceded by single-blind run-in and followed by a24-week Open-label Extension

Intervention

Investigational drug (BLU-5937 25 mg or BLU-5937 50 mg) or matching placebo will be
taken orally, twice daily. All BLU-5937 tablets and their matching placebo tablets are identical in shape
and color but they differ in size.
Single-blind Placebo Run-in:

• All participants: one (1) 25 mg matching placebo tablet and one (1) 50 mg matching placebo
tablet will be administered twice daily orally.
Randomized Double-blind Treatment (3 treatment arms):
• BLU-5937 25 mg group: one (1) 25 mg active tablet and one (1) 50 mg matching placebo tablet
will be administered twice daily, orally
• BLU-5937 50 mg group: one (1) 50 mg active tablet and one (1) 25 mg matching placebo tablet
will be administered twice daily orally
• BLU-5937 Placebo group: one (1) 25 mg matching placebo tablet and one (1) 50 mg matching
placebo tablet will be administered twice daily orally.
Open-label Extension:
• All participants: one (1) 50 mg active tablet.

Study burden and risks

Subject*s participation in this study will last 85 weeks and consists of a screening period, treatment period and a follow-up period. During the treatment period, subjects will need to visit the study site every 4 weeks. There will be a total of 19 visits to the study center during the study. The study center staff will also set up 6 phone calls. Day 546 participants will undergo efficacy and safety follow-up evaluations.
Based on nonclinical toxicity studies, the major organs/systems identified for toxicity were the
gastrointestinal (GI) tract, liver, kidney, hematopoietic system, ocular, and male reproductive
organs.

Refractory chronic cough can seriously impair quality of life. The disabling effects of chronic
cough are understandable, given that patients with RCC can cough up to hundreds of times per
hour for months to years. The treatment options for RCC are limited and not optimal due to either
low efficacy (over-the-counter drugs) or poor tolerance (gabapentanoids/opioids).

Taking into account the measures taken to minimize risk to participants in this study, the potential
risks identified in association with BLU-5937 are justified by the anticipated benefits that may be
afforded to participants with RCC. The overall benefit-risk is considered favorable.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Between 18 and 80 years of age inclusive, at the time of signing the informed consent 2. Capable of understanding the written informed consent as described in Appendix 1, Section 10.1.5, which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and in this protocol, provides signed and witnessed written informed consent, and agrees to comply with protocol requirements including being available for the duration of the study 3. After investigation into potential underlying causes of chronic cough, have a diagnosis of RCC defined as: a) insufficient improvement in cough after treatment for the underlying condition(s) contributing to their cough, OR b) unexplained cough for which an underlying condition has not been determined despite adequate investigation with diagnostic tests and trials of therapy 4. The Eligibility Adjudicator

assessment confirms prior to randomization that the participant*s history meets diagnostic criteria for RCC 5. Persistent cough for >= 1 year prior to Screening 6. Chest radiograph or computed tomography of the thorax within the last 5 years from Screening and following the onset of chronic cough that does not show any abnormality considered to be significantly contributing to the chronic cough in the opinion of the Investigator

7. Participants must meet the following cough frequency criteria:
a) Participants in the Overall Efficacy population must have a 24-hour cough frequency of >=16 coughs/h at Screening and >=20 coughs/h at Baseline (Day -7), or between >=8 and <40 coughs/h at Screening and between >=8 and <20 coughs/h at Baseline (Day -7). Approximately 25% of participants with a 24-hour cough frequency between >=8 and <40 coughs/h at Screening and between >=8 and <20 coughs/h at Baseline will be enrolled (approximately 63 participants per treatment arm).
When this 25% threshold has been reached, only participants with a 24hour cough frequency of >=16 coughs/h at Screening and >=20 coughs/h
at Baseline will be enrolled (approximately 187 participants per treatment arm).
b) Participants in the Exploratory Efficacy population will have a
24-hour
cough frequency between >0 and <16 coughs/h at Screening and a 24hour cough frequency between >0 and <8 coughs/h at Baseline (Day 7). The exploratory population will enroll participants until up to 25 per treatment arm has been reached.
8. A score of >= 40 mm on the CS-VAS at Screening and Baseline (Day 1) 9. A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least 1 of the following conditions applies: i) Not a woman of childbearing potential (WOCBP) as defined in Appendix 5. OR ii) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 from Screening through the Follow-Up Visit (2 weeks after the last dose of study drug). Note: WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline and must use a highly effective contraception method from Screening through the Follow up Visit (highly effective methods of birth control in this study include: combined estrogen and progestogen containing or progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine
hormone-releasing system, bilateral tubal occlusion, vasectomized partner or same sex partner) or agrees to total abstinence,
defined as refraining from heterosexual intercourse, as the preferred and usual lifestyle.) 10. Male participants must agree to use contraception as detailed in Appendix 5 of this protocol from Screening through the Follow-Up Visit and make no donation of sperm from Screening until 3 months after the last dose of study treatment.

Exclusion criteria

1. Current smoker or vaper or current use of tobacco smoke, cannabis smoke, or nicotine vapors 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 chronic obstructive pulmonary disease, bronchiectasis, chronic bronchitis, cystic fibrosis, pulmonary sarcoidosis, idiopathic pulmonary fibrosis, or other significant or progressive airway/respiratory disorder that might affect cough based on clinician assessment 4. History of upper and/or lower respiratory tract infection or significant change in pulmonary status within 28 days of Screening or during Screening or the Single-blind Placebo Run-in 5. Laboratory confirmed severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection at Screening or during Single-blind Placebo
Run-in. Medical history of malignancy and treatment completed <= 5 years prior to Screening except for adequately treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or carcinoma in situ of the cervix 7. History of a diagnosis of drug or alcohol dependency or abuse within the last 3 years, per Investigator assessment, or a positive urine opioid drug screen result at Screening. Stable opioid treatment for non-cough indication is permitted (refer to Appendix 4 of the study protocol) 8. Positive serological test for HIV, hepatitis B, or hepatitis C at
Screening
Note: Participants with positive hepatitis B or C serology will have confirmatory testing. Participants with HIV on stable treatment with undetectable viral load are acceptable if the participant otherwise meets entry criteria. Participants with positive hepatitis C antibody test due to prior resolved disease who have successfully completed a course of antiviral therapy can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained and if the participant otherwise meets entry criteria
9. Previous participation in an investigational study of BLU-5937 For the full list of exclusion criteria please refer to the study protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-08-2023
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BLU-5937
Generic name:	BLU-5937

Ethics review

Approved WMO Date:	05-12-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-05-2023
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-08-2023
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-12-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-12-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-04-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-513460-26-00
EudraCT	EUCTR2022-000223-20-NL
CCMO	NL82941.100.22