BLU-5937 for Refractory Chronic Cough: Positive FDA End of Phase 2 Meeting and its CALM Phase 3 Program Design

JULY 12, 2022

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Positive FDA End-of-Phase 2 Meeting and Announcing CALM Phase 3 Program

Positive FDA End-of-Phase 2 meeting with clear path forward for BLU-5937's CALM Phase 3 program in refractory chronic cough

- **CALM Phase 3 Program designed to support approval of BLU-5937 for treatment of refractory chronic cough (RCC):**
  - ✓ Two pivotal Phase 3 trials, CALM-1 and CALM-2, with 3 expected arms: 25mg, 50mg and placebo BID
  - ✓ Primary efficacy endpoint of 24H cough frequency at 12 weeks in CALM-1 and 24 weeks months in CALM-2
    - ➢ FDA alignment on using primary efficacy endpoint in population enriched for baseline cough frequency, similar to successful SOOTHE Phase 2b trial
  - ✓ Safety database supported by randomized extension of CALM-1 and open label extension of CALM-2
  - ✓ First patient enrollment in CALM-1 expected in Q4 2022 and pivotal topline data from CALM-1 expected in 2H 2024
  - ✓ Use of VitaloJAK cough monitoring system in CALM Phase 3 program; preliminary validation (n=30) study results using historical SOOTHE Ph2b data demonstrated 98.4% sensitivity

- **Well financed for Phase 3 following positive FDA End of Phase 2 meeting**
  - ✓ $234M as of March 31st provides cash runway to Q4 2024 and through top-line data from CALM-1

CALM Program: Study Design

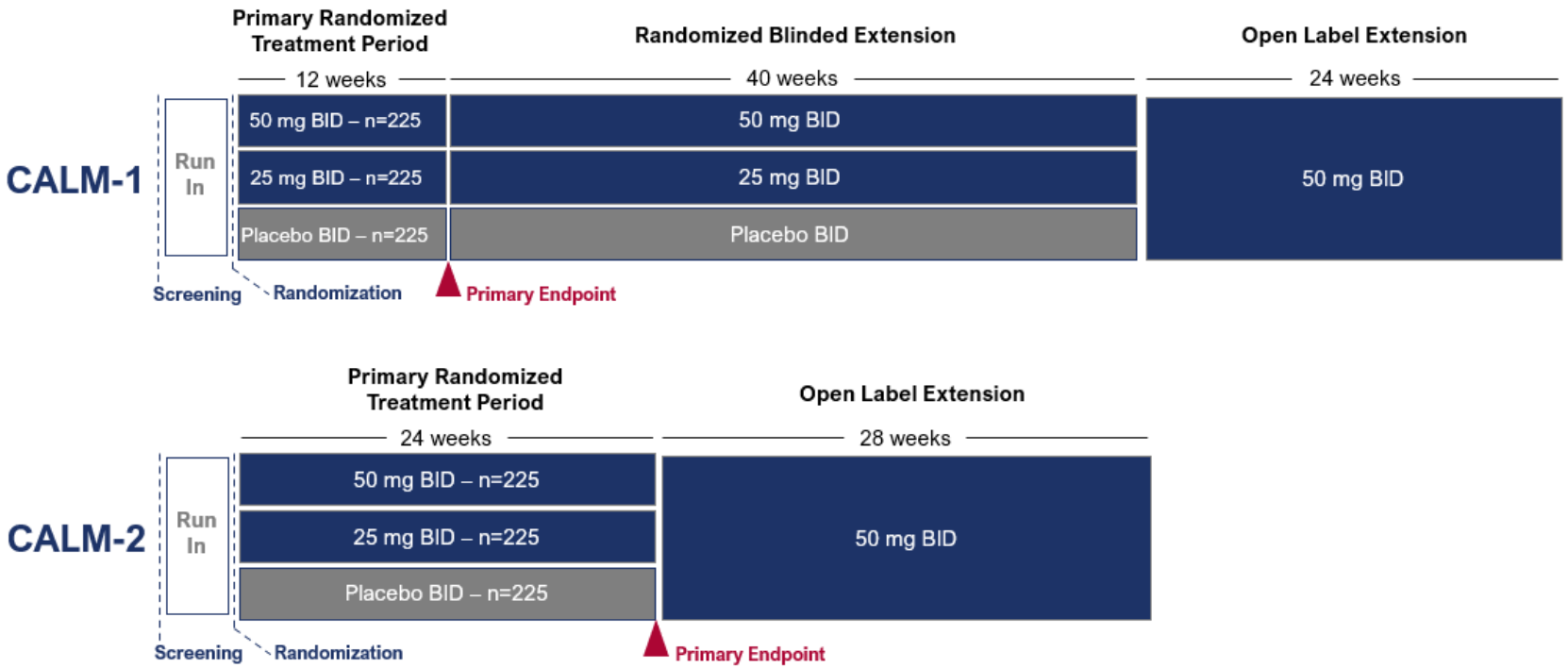
Two randomized, double-blind, placebo-controlled parallel arm trials with 2 active doses

POPULATION

- Refractory/unexplained chronic cough
- Cough ≥1 year
- Enriched for baseline cough frequency
- CALM-1 and CALM-2: ~675 participants each

PRIMARY EFFICACY ENDPOINT

- 24H cough frequency (CF) in enriched population



CALM Program: Enrichment Strategy

CALM-1 and CALM-2 populations to be enriched for baseline cough frequency

PRIMARY POPULATION

- ≥ 20 coughs/h (24H CF)
- Equivalent to ≥25 cough/h (awake CF) population in successful SOOTHE Phase 2b trial

EXTENDED POPULATION

- <20 coughs/h (24H CF)

PRIMARY EFFICACY ENDPOINT: COUGH FREQUENCY IN PRIMARY POPULATION (90% POWER)

- 24H cough frequency vs placebo in Primary Population

SECONDARY EFFICACY ENDPOINTS (80% POWER)

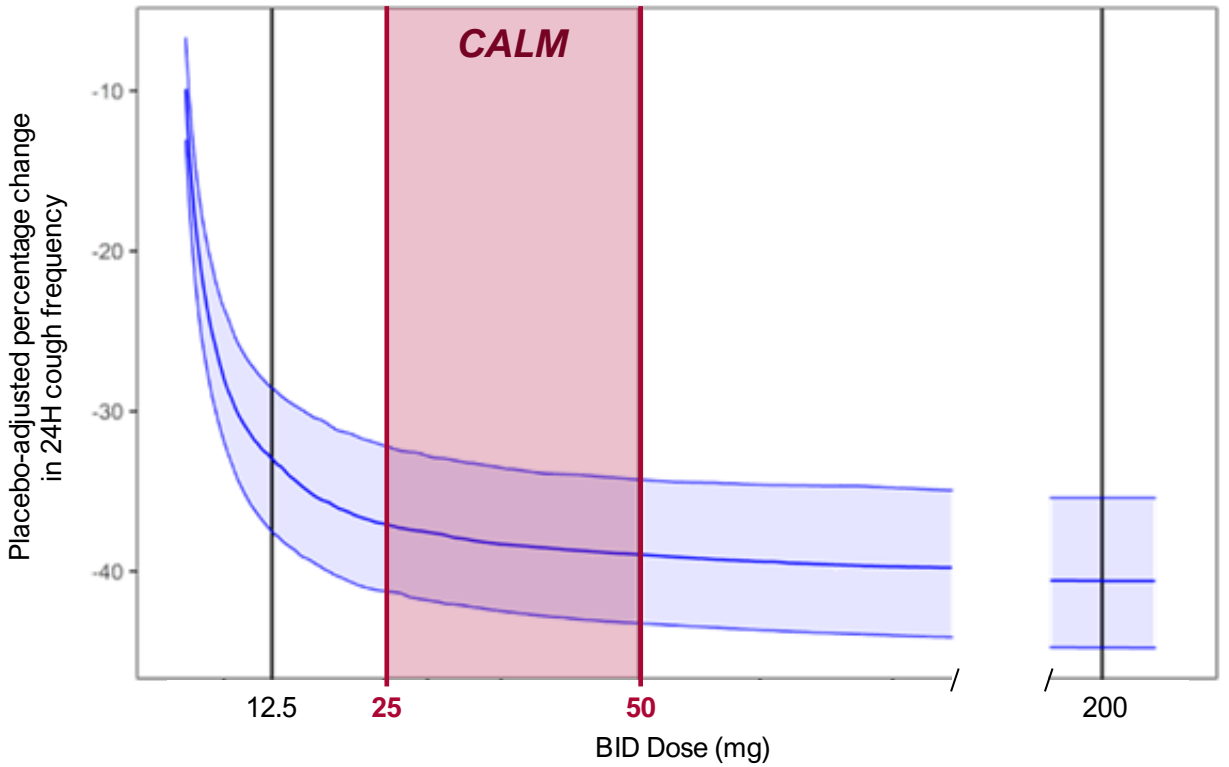
- Leicester Cough Questionnaire (LCQ), Cough Severity VAS (CS-VAS) and Chronic Cough Diary (CCD) in the Primary Population
- 24H cough frequency vs placebo in Overall Population (Primary Population + subpopulation of Extended Population)

CALM Phase 3: Dose Selection

Well supported clinical rationale for 25 and 50mg BID dose selection:

- No dose response observed between 25 and 200mg BID in RELIEF Ph2a study
- 50mg BID lowest optimal dose in SOOTHE Phase 2b study
  - 50 and 200mg BID achieved 34% placebo-adjusted reduction in cough frequency
- >90% of maximum predicted effect using PK/PD modeling in SOOTHE Phase 2b trial for 25 and 50mg BID doses:
  - 91.3% for 25mg BID
  - 96.3% for 50mg BID

Model-Predicted Relative Change From Baseline In 24H Cough Frequency After Multiple BLU-5937 BID Dosing



Dose range in SOOTHE

Dose range in RELIEF

CALM Phase 3: Statistical Methodology

- Statistical consultants recommended and FDA was aligned with using the negative binomial (NB) statistical method to analyze cough count data in CALM Phase 3 Program
- NB expected to have a better statistical fit for count data like cough frequency
  - Previous method of log-transformation of cough data does not provide optimal statistical fit
  - Well documented use[1-7] in trials with analysis of count data
- In BELLUS clinical datasets, NB provides better statistical fit:
  - Better manages variability and increases power
  - Minimal impact of extreme outliers

SOOTHE Primary Efficacy Endpoint (Main Population): Placebo-adjusted 24H cough frequency at Day 28

	Negative Binomial		Log Transformation	
Dose	**Δ**	**p-value**	**Δ**	**p-value**
12.5 mg	**-28%**	*0.0013*	**-21%**	*0.098*
50 mg	**-33%**	*0.0005*	**-34%**	*0.0033*
200 mg	**-32%**	*0.0021*	**-34%**	*0.0047*

SOOTHE Secondary Endpoint (Main + Exploratory Population): Placebo-adjusted 24H cough frequency at Day 28

	Negative Binomial		Log Transformation	
Dose	**Δ**	**p-value**	**Δ**	**p-value**
200 mg	**-23%**	*0.012*	**-20%**	*0.078*

SOOTHE Main Population: ≥25 awake c/h

SOOTHE Exploratory Population: 10-<25 awake c/h

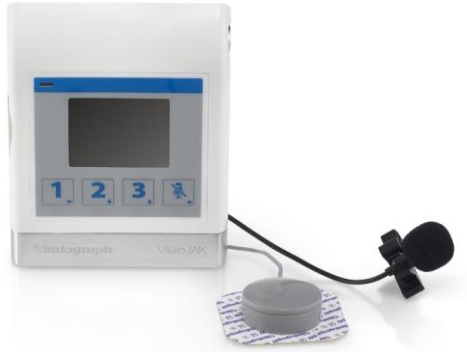
In CALM Phase 3, use of Negative Binomial is expected to provide better power to detect treatment benefit and reduce risk of outliers skewing results

1. Ortega et al. (2014) N Engl J Med 371(13):1198-207. 2. Castro et al (2015) Lancet Resp Med 3(5):355-66. 3. Pavord et al. (2017) N Engl J Med 377(17):1613-1629. 4. Criner et al. (2019) N Engl J Med 381(11):1023-1034. 5. Smith et al. (CHEST) 2020 157(1):111-118. 6. Miller (2020) JAMA Neurol. 77(5):613-621. 7. Thiele (2021) JAMA Neurol 2021 Mar 1;78(3):285-292.

CALM Phase 3: VitaloJAK Cough Monitoring System

- VitaloJAK is the cough recording and counting system used to capture the 24H cough frequency data in most cough trials
  - Used in BLU-5937 and gefapixant RCC trials
  - Will be used in the CALM Phase 3 program
- The Company and FDA aligned on validation of VitaloJAK cough frequency measurement to support the potential BLU-5937 New Drug Application
  - Validation study comparing compressed vs non-compressed recordings in SOOTHE Phase 2b trial participants is on-going
  - Preliminary results from the first 30 recordings demonstrated a sensitivity of 98.4% with no systematic errors present
  - Complete results are expected in Q4 2022/Q1 2023
  - Validation work has no impact on start of Phase 3

VitaloJAK Cough Monitoring Device

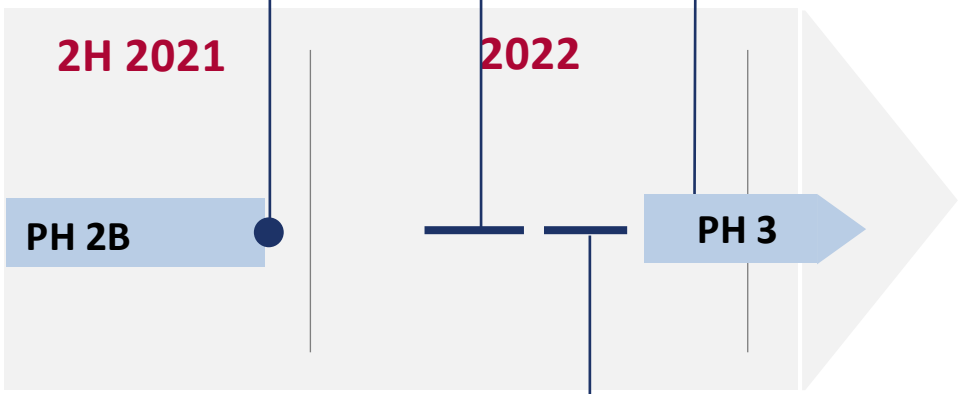


CALM Phase 3: Clinical Development Milestones and Expected Next Steps

December 13, 2021
SOOTHE Phase 2b
Topline Results

June 2022
End-of-Phase 2
Meeting with FDA

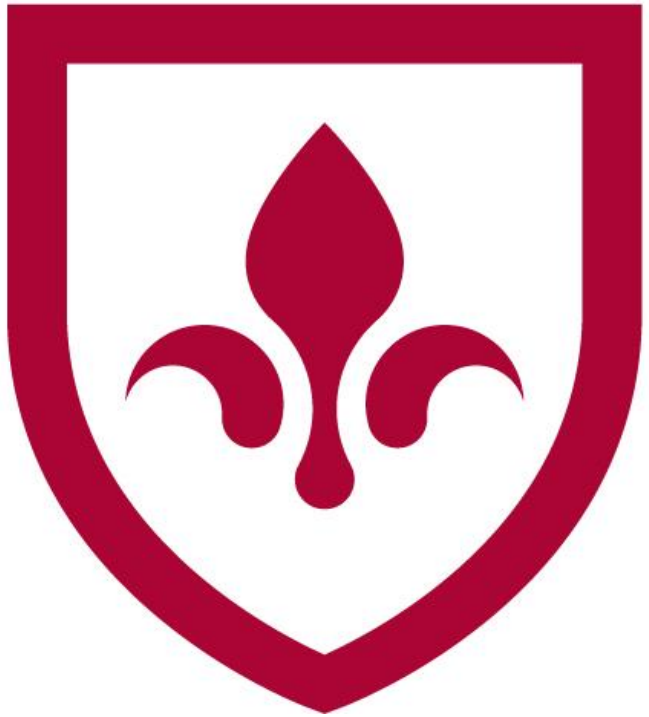
4Q 2022
Expected First Patient
Enrolled in Phase 3
CALM-1 Trial



3Q 2022
Expected Final Protocols
(IND Submission)
EMA Feedback

Topline results from CALM-1 Phase 3 trial expected in 2H 2024

BELLUS Today



- **Potential BLU-5937 best-in-class profile** for the treatment of refractory chronic cough, a large and growing market with limited competition
- **Positive FDA End-of-Phase 2 meeting** with clear path forward for BLU-5937's Phase 3 CALM program in RCC
- **World-class team** focused on delivering value to patients and shareholders
- **100% economics** and **global rights** to BLU-5937 intellectual property
- **Potential for building pipeline** targeting cough hypersensitivity in additional cough indications