Model-Based Dose Selection for Phase 3 Trials of the Selective P2X3 Antagonist Camlipixant in Refractory Chronic Cough

Gahir S, Garin M, Harvey L, Yang T, Garceau D, Bonuccelli C and Chauret N

Bellus Health Inc, Laval, QC, Canada and Bellus Health Inc. Wilmington, DE, USA

Introduction

- Refractory Chronic Cough (RCC) is a cough that persists for 8 weeks or more despite adequate treatment of all identifiable associated diseases or without identifiable cause.1,2
- P2X3 antagonists have shown promise in clinical trials as potential treatment for RCC.
- The selective P2X3 antagonist camlipixant (BLU-5937) has been evaluated for treatment of RCC in two Phase 2 clinical trials.
- RELIEF was a Phase 2a, 2-period crossover, forced dose-escalation study with camlipixant 25, 50, 100, and 200 mg BID and placebo. Clinically meaningful and significant reductions in cough frequency were observed in participants with a baseline awake cough frequency ≥20 coughs/h. No clear dose response was observed (Figure 1).
- SOOTHE was a Phase 2b, 4-week, parallel-arm study with camlipixant 12.5, 50, and 200 mg BID and placebo. A dose-response was observed between the 12.5 and 50 mg BID doses in the main population (awake cough frequency ≥25 coughs/h), but no appreciable increase in response was observed between 50 mg and 200 mg BID doses (Figure 2).
- The overall safety and tolerability of camlipixant in Phase 2 was similar to placebo apart from the frequency of taste disturbance adverse events. No dose effect was seen for incidence and severity of adverse events.

Methodology

Dataset Construction + Exploratory Analysis
Phase 1: (n=72) [NCT03638180]
Phase 2a: RELIEF (n=61)

Population PK Model & Covariate Analysis
PK data: FIH-SAD/MAD and RELIEF studies optimized in NONMEM
Stepwise forward additive ($p<0.05$) & backward elimination ($p<0.01$) approach
FIH=first in human; SAD=single ascending dose; MAD=multiple ascending dose

Update Model – Add PK data
Phase 2b: SOOTHE (n=211)

E-R Analysis
PK endpoint
- Simulated profiles on Day 15 & 29

Efficacy endpoints:
Change from baseline to Day 15 & (end of treatment) in:
- 24-h cough frequency (Day 28)
- CS-VAS (Day 29)

Simulations for Phase 3 Study Dose selection
Virtual population (n-1000)
Monte Carlo simulation for dose prediction

Efficacy Prediction Analyses

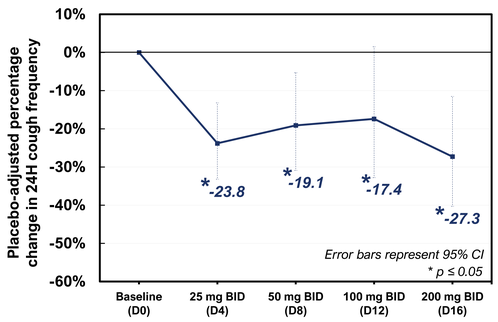

Figure 1. Placebo-adjusted Change from Baseline in 24H Cough Frequency in ≥ 20 coughs/h$_{baseline}$ subgroup in RELIEF

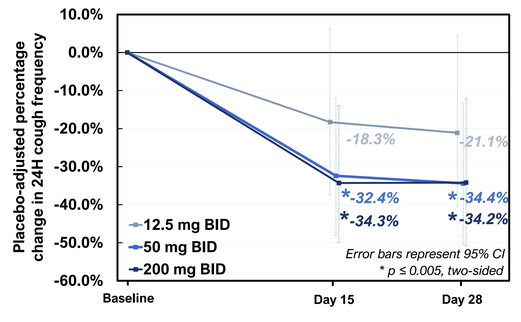

Figure 2. Placebo-adjusted Change from Baseline in 24H Cough Frequency in SOOTHE

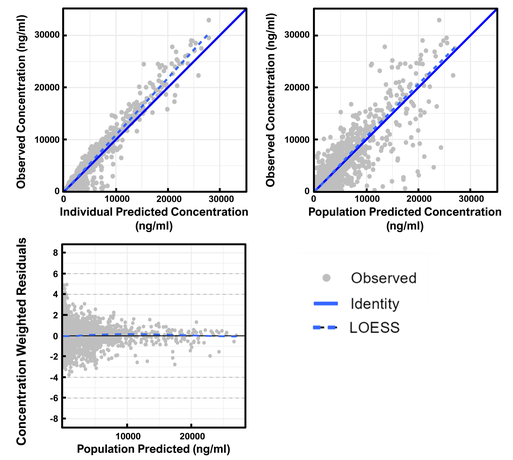

Figure 3. Goodness-of-fit Plots

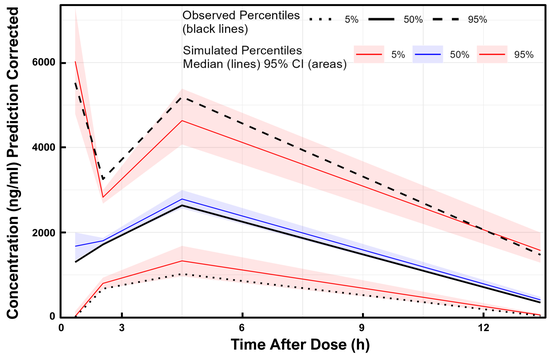

Figure 4. Visual Predictive Check Plot

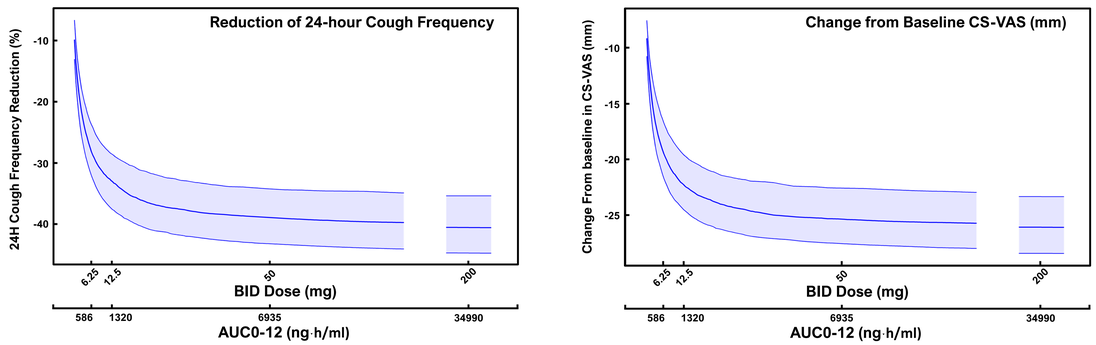

Figure 5: Predicted Response in Subjects with RCC after Multiple BID Administrations of Camlipixant

Safety & Tolerability

- In RELIEF and SOOTHE , there was a similar incidence of treatment-emergent adverse events reported for placebo and camlipixant and no treatment-emergent serious adverse events occurred in either study.
- In RELIEF, no dose-related patterns of adverse events were seen and there were no clinically significant effects on vital signs, electrocardiogram or laboratory measures.
- In SOOTHE, taste disturbance adverse events were reported ≤6.5% for any camlipixant group.
- There were no complete nor partial taste loss at any camlipixant dose in SOOTHE, and there were no discontinuations due to taste disturbances.

Discussion

- A two-compartment, mixed absorption kinetics model with linear elimination was found to adequately describe exposure of camlipixant based on goodness-for-fit and visual predictive check.
- No intrinsic or extrinsic co-variates impacting dose selection were identified.
- The area under the plasma concentration-time curve during dosing interval was identified as an appropriate predictor of response.
- A sigmoidal I_{max} function was found to best describe the change from baseline in 24-h cough frequency and cough severity visual analog scale (CS-VAS).
- E-R modeling predicted that camlipixant 50 mg BID would provide near maximal reduction in cough frequency and CS-VAS.
- The model also indicated that camlipixant 25 mg BID was the lowest dose level anticipated to achieve >90% of the maximum potential reduction in cough frequency and CS-VAS.

Conclusions

- In the absence of dose-related safety findings, based on population pharmacokinetic E-R analysis, the 25 and 50 mg BID doses of camlipixant were predicted to achieve efficacy in cough frequency reduction and CS-VAS. Additionally, doses above 50 mg were not predicted to achieve additional benefit.
- Thus, these doses were deemed to be the most appropriate to study in Phase 3 pivotal trials of camlipixant in RCC.

References

1. Morice et al. Eur Respir J. (2020) 55(1):1901136.
2. Irwin et al. Chest. (2018) 153(1):196-209.

RELIEF: NCT03979638 / SOOTHE: NCT04678206