BLU-5937: *A Highly Selective P2X3 Homotrimeric Receptor Antagonist, Exhibits Excellent Pharmacokinetic and Safety Profile Including Improved Taste Safety Profile in Healthy Subjects*

Denis Garceau[1], Nathalie Chauret[1] and Laurent Harvey[1]

[1]Bellus Health Inc.

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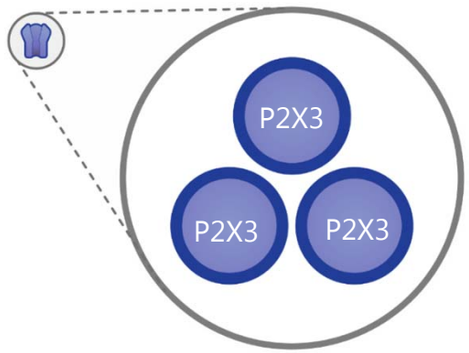
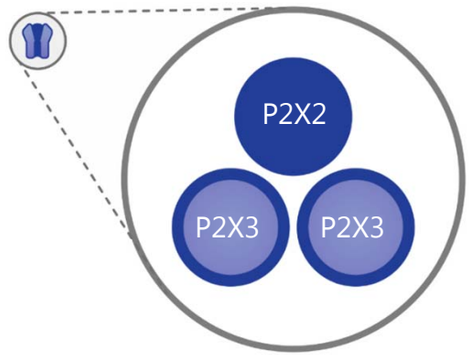
TARGETING P2X3 TO TREAT CHRONIC COUGH

BLU-5937: High Potency (IC_{50} = 25 nM) and Selectivity (1500X) for P2X3 vs P2X2/3



P2X3 homotrimeric receptors are linked to cough hypersensitivity

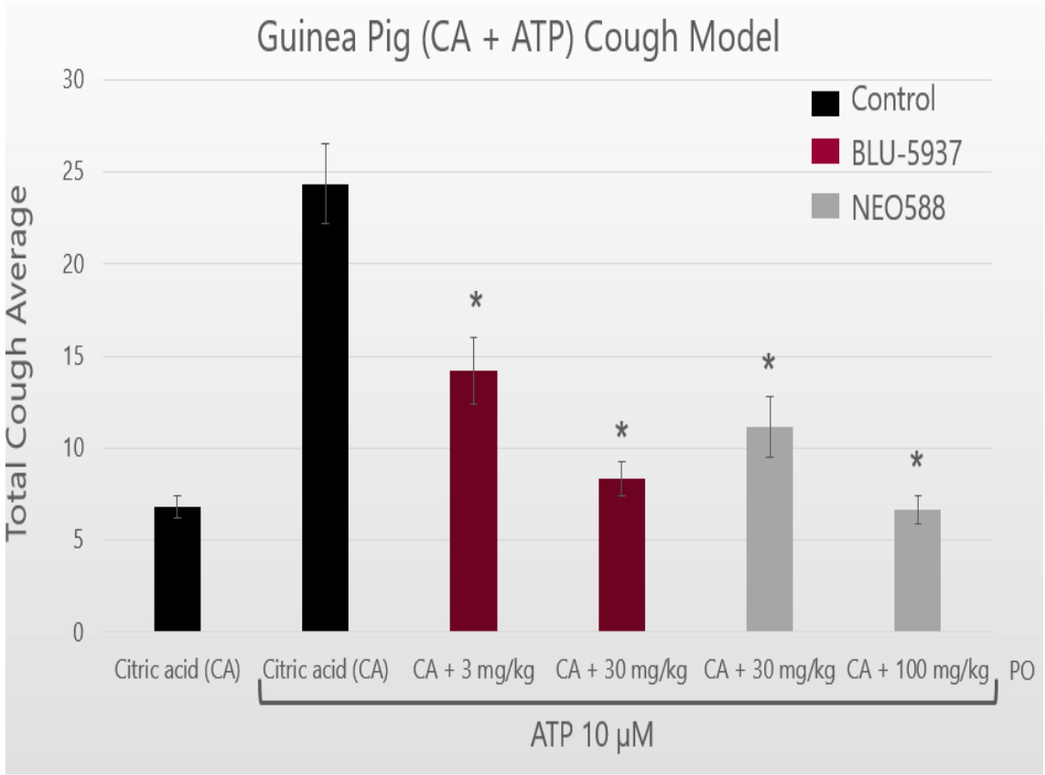


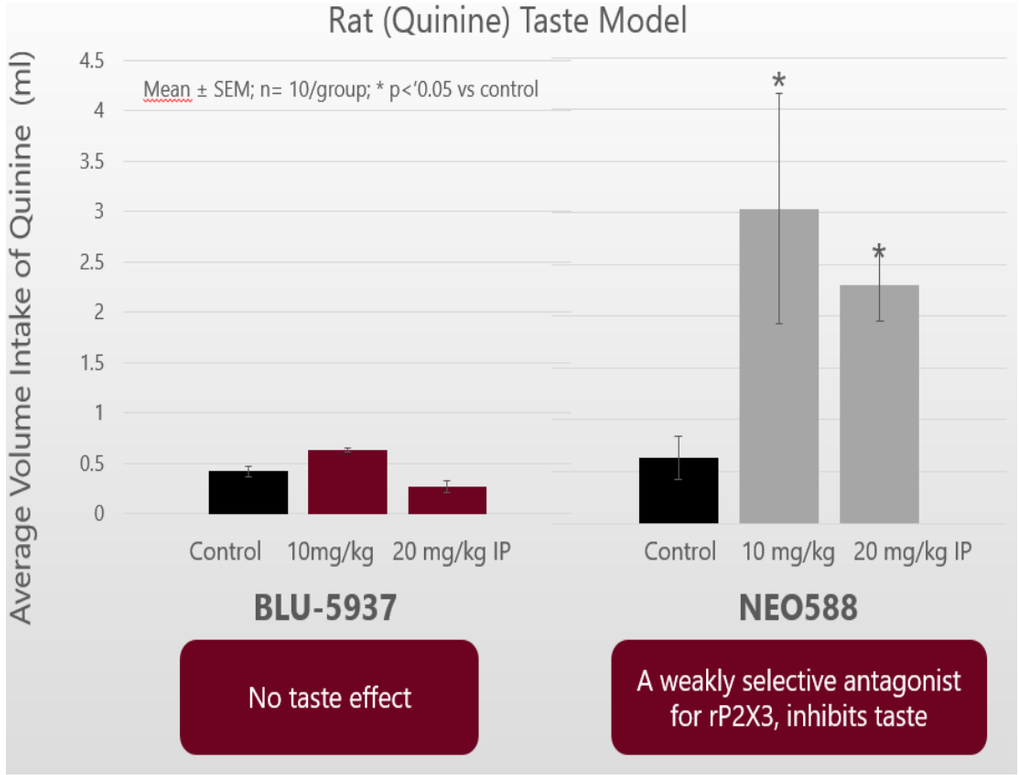
P2X2/3 heterotrimeric receptors are linked to taste function

Hypothesis:

Selective inhibition of P2X3 homotrimeric receptors would reduce cough with little or no impact on taste perception

BLU-5937: PRECLINICAL PROOF-OF-CONCEPT





BLU-5937 reduced cough at doses that blocked P2X3 but not P2X2/3 receptors AND no taste effect

BLU-5937: PHASE 1 STUDY DESIGN

Key Objectives

- To assess safety, tolerability (including taste effects) and pharmacokinetic profile of BLU-5937
- Randomized, double-blind, placebo-controlled
- N=90 healthy adult subjects

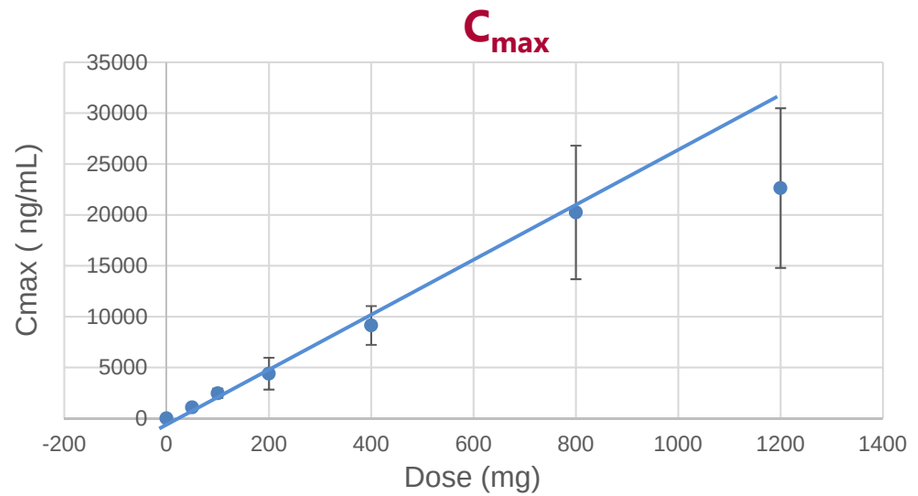
Single Ascending Dose (SAD)

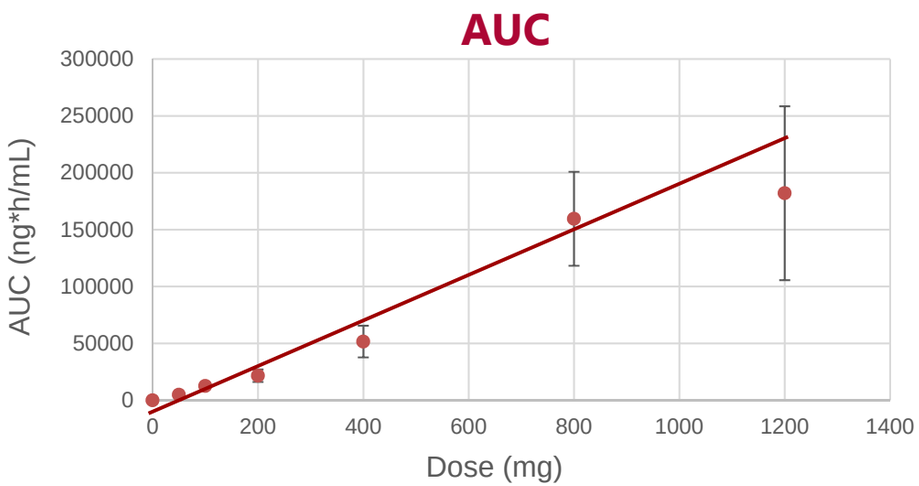
- 6 cohorts of 10 subjects (8 active: 2 placebo)
- Single oral doses of 50mg to1200mg
- Food interaction tested in 1 cohort (200mg)

Multiple Ascending Dose (MAD)

- 3 cohorts of 10 subjects (8 active: 2 placebo)
- Doses of 100, 200 and 400mg BID for 7 days

BLU-5937: EXCELLENT PK PROFILE IN HEALTHY SUBJECTS





Observations:

- BLU-5937 is rapidly absorbed (T_{max} ~1h)
- Plasma half-life 4-9 hours supports BID dosing
- No significant effect of food on PK
- No significant systemic accumulation over 7 days
- Predicted therapeutic dose: 50-100 mg BID

BLU-5937: SAFE AND WELL TOLERATED

Incidence of Most Frequent Adverse Events (>5% Incidence) in All Cohorts (SAD + MAD)

AEs N (%)	Placebo (n=18)	50mg (n=8)	100mg (n=16)	200mg (n=16)	400mg (n=16)	800mg (n=8)	1200mg (n=8)	Total BLU-5937 (n=72)
Taste alteration	0 (0%)	0 (0%)	1 (6%)	0 (0%)	6 (38%)	5 (63%)	2 (25%)	14 (19%)
Headache	1 (6%)	0 (0%)	2 (13%)	1 (6%)	1 (6%)	2 (25%)	2 (25%)	8 (11%)
Hypoaesthesia	0 (0%)	0 (0%)	0 (0%)	3 (19%)	2 (13%)	3 (38%)	0 (0%)	8 (11%)
Dizziness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (13%)	1 (13%)	1 (13%)	4 (6%)
Nausea	1 (6%)	0 (0%)	0 (0%)	1 (6%)	1 (6%)	2 (25%)	2 (25%)	6 (8%)
Dyspepsia	0 (0%)	0 (0%)	1 (6%)	0 (0%)	2 (13%)	1 (13%)	0 (0%)	4 (6%)

- No serious adverse event; >80% of AEs were mild; no significant effect on vital signs, ECG, laboratory
- Potential P2X3 class-related side effects include: taste effects, hypoaesthesia
- One subject had mild liver enzyme elevation (400mg BID) that normalized at follow up; not associated with an increase in bilirubin

LOW INCIDENCE OF TASTE EFFECT AT PREDICTED THERAPEUTIC DOSES

Incidence of Taste AEs (All Cohorts SAD+MAD)

	50 mg (n=8)	100 mg (n=16)	200 mg (n=16)	400 mg (n=16)	800 mg (n=8)	1200 mg (n=8)
Dysgeusia	0 (0%)	1 (6.3%)	0 (0%)	6 (37.5%)	5 (62.5%)	2 (25%)
Hypogeusia	0 (0%)	0 (0%)	0 (0%)	1 (6.25%)	1 (12.5%)	0 (0%)
Ageusia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ratio plasma C_{max} / IC_{50} hP2X3	12.9	29.4	52.4	108.7	240.9	269.4
Ratio plasma C_{max} / IC_{50} hP2X2/3	0.01	0.03	0.05	0.11	0.25	0.28

- One / 24 subject (4.2%) reported taste effect at the anticipated therapeutic doses (50-100 mg)
- No complete taste loss (ageusia) at any dose
- Increase incidence of taste effect correlates with inhibition of P2X2/3 at supra-therapeutic doses (400-1200 mg)

TASTE ADVERSE EVENTS: LIMITED, TRANSIENT, & SPORADIC

Multiple Ascending Dose Study (7-day dosing)

5 / 24 subjects experienced taste alteration
(4 at 400 mg BID and 1 at 100 mg BID)

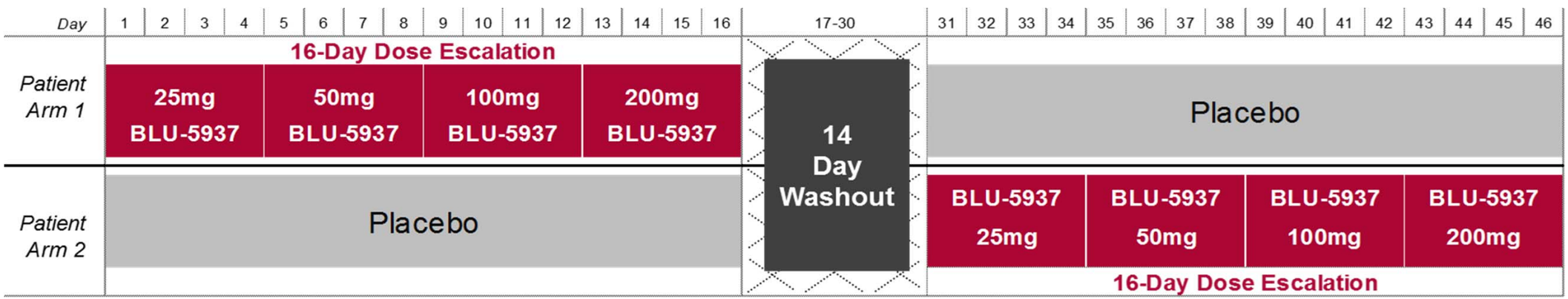
All 5 subjects experienced the taste event on their first dose (Day 1)

2 had no other episode of taste event during the 7-day dosing period

3 had only one second episode of taste event during the 7-day dosing period

BLU-5937: PHASE 2 PROOF-OF-CONCEPT STUDY [1]

- ~50 unexplained/refractory chronic cough patients; at >1 year coughing
- 12 sites in UK and USA
- 4 dose levels with forced escalation at 4-day intervals (25/50/100/200mg po, twice daily)
- Primary endpoint: Reduction in awake cough frequency using cough recorder
- Safety, tolerability (including taste effect)



[1] **Phase 2 study initiation expected mid-2019; with topline data in mid-2020**

CONCLUSIONS

BLU-5937: Highly Selective P2X3 Antagonist with Excellent Drug-Like Characteristics

- Excellent pharmacokinetic profile
- Projected optimal therapeutic doses of 50-100mg BID
- Safe and well tolerated
  - Low incidence of mild, transient and sporadic taste events (<5%) at predicted therapeutic doses
- Phase 1 results support moving forward with Phase 2 study in mid-2019