BLU-5937 Update and Chronic Cough Key Opinion Leader Event

September 20, 2017
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BLU-5937 Overview

BLU-5937 Background
- Developed at AstraZeneca in P2X3 antagonist discovery program, then NEOMED Institute
- Global rights licensed by BELLUS in February 2017

P2X3: validated target for chronic cough
- Merck acquired Afferent Pharma’s P2X3 antagonist program in 2016 for US$500M based on positive Phase 2 data
- Problematic side effect profile: 80% of patients experienced taste disturbance

BLU-5937: Potentially best-in-class P2X3 antagonist
- Potential for differentiated product profile with improved efficacy and reduced/no taste disturbance
- Clear, efficient path to demonstrate superiority
A Review of Chronic Cough
Prof Jacky A. Smith MB, ChB, FRCP, PhD
University of Manchester
Chronic Cough

Characteristics

Cough lasting ≥ 8 weeks, associated with:

- Pulmonary diseases (asthma, COPD, IPF)
- Extra-pulmonary disorders (allergic rhinitis, gastro-oesophageal reflux)
- Side effect of certain drugs
- No identifiable cause

Cough frequency can be high (10-100s times per hour) with lengthy duration (months or years)
Prevalence of Chronic Cough

UK Postal Questionnaire Survey

Danish Population Based Cohort

Ford et al Thorax 2006;61;975-979

Colak et al Chest 2017;152:563-573
Major Impact on Patients with Refractory / Unexplained Chronic Cough

Physical complications
- Fatigue
- Sleep deprivation
- Vomiting
- Incontinence
- Headache
- Chest pain
- Rib fracture

Social complications
- Interference with lifestyle, work & leisure
- Difficulty conversing
- Embarrassment of coughing in public

Psychosocial complications
- Anxiety
- Anger
- Depression
- Distress

Significant disruption in day to day life for chronic cough patients
### Few Treatment Options for Chronic Refractory/Unexplained Cough

<table>
<thead>
<tr>
<th>Opioids</th>
<th>Benzonatate</th>
<th>Dextromethorphan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Can be efficacious</td>
<td>Anesthetize the stretch receptors in the lungs</td>
<td>Key ingredient in OTC cough suppressants</td>
</tr>
<tr>
<td>Limited use due to side</td>
<td>Temporary relief</td>
<td>Limited efficacy</td>
</tr>
<tr>
<td>effects and potential for</td>
<td>Potential serious side effects</td>
<td></td>
</tr>
<tr>
<td>addiction</td>
<td>if capsule broken</td>
<td></td>
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</table>

**Gabapentin/pregabalin**

- Neuromodulators with variable efficacy and significant CNS side effects

**Speech Therapy**

- Has shown some efficacy especially in combination with pharmacotherapy

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Significant need for efficacious chronic cough therapy that is non-narcotic and non-sedating
P2X3 Receptor: Rational Target for Refractory/Unexplained Chronic Cough

Sensory stimuli: heat, cold, acid, chillis, smoke, and chemicals.

Larynx, Trachea, & Bronchus: ATP released due to sensory stimuli.

Brain: P2X3 receptor activated by ATP.

Jugular: Vagus (X) nerve pathway to the brain.

Cough: P2X2 vs. P2X3 expression adapted from Kwong et al. 2008 AJP Lung cell Mol Physiol 295 L858-65

Lung cell Mol Physiol 295 L858-65
Targeting P2X3 is an efficacious strategy for treating chronic cough.

**Merck’s MK-7264 - P2X3 Antagonist**

Reduction in Awake Cough Frequency
(from Baseline Compared to Placebo)

- **Placebo**
- **7.5 mg**
- **20 mg**
- **50 mg**

* p<0.05 vs. placebo

Phase IIb (253 patients; 12 week study) showed reduction in awake cough frequency of **84%** vs baseline **37%** vs placebo at 50mg dose

MK-7264: Significant Adverse Taste Effect

Taste effect likely due to low selectivity for P2X3; MK-7264 also inhibiting P2X2/3, particularly at 50mg dose

At therapeutic dose (50 mg BID):

- ~80% of patients reported taste alteration
- ~40% of patients reported very/extremely bothersome taste effect

# Clinical Studies in Chronic Cough

<table>
<thead>
<tr>
<th>Design</th>
<th>Endpoints</th>
<th>Regulatory</th>
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</thead>
<tbody>
<tr>
<td>Crossover design is very efficient for Phase 2 proof of concept</td>
<td>Reduction in awake cough frequency as measured by cough monitor</td>
<td>At least 2 large Phase 3 studies required for approval</td>
</tr>
<tr>
<td>Crossover design requires limited number of patients and short duration with objective cough monitoring</td>
<td>Good correlation between cough frequency and patient reported measures</td>
<td>Primary endpoint likely to be cough frequency reduction using validated cough recorder</td>
</tr>
<tr>
<td>Crossover design results have been confirmed in longer term study</td>
<td>Potential for important placebo effect in parallel group studies</td>
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Recent learnings in clinical studies have provided clear path for development of chronic cough drugs
TRP modulators

- Main target (TRPV1) has shown serious toxicity issues with first compounds
- Two recent Phase 2 trials in chronic cough patients showed effect on cough challenge but not cough frequency

NK1 antagonists

- Repurposed class initially developed for depression
- Also target afferent nerve signaling especially at first synapse
- Limited clinical validation in chronic cough

P2X3 antagonists

- Drug class inhibiting afferent pathway signals from respiratory tract
- Most promising and competitive novel class of antitussive medicine

nAChR modulation

- CNS acting modulators, could inhibit cough signal processing in the brain
- Limited mechanistic characterization in humans
BLU-5937 for Chronic Cough
Dr. Denis Garceau
BELLUS Health
Strong drug candidate profile with potential to be best in P2X3 class

- Twice Daily Oral Dosing Expected
- High Potency and Selectivity for P2X3
- No safety findings of concern
- Broad and comprehensive IP to 2034
- Targeting ~2.7M US Patients
P2X3 and P2X2/3 Roles in Cough and Taste

ATP-gated ion channels that transmit sensory signals, function in two predominant trimer structures:

- **P2X3 homotrimers** have primary role in **cough reflex**
- **P2X2/3 heterotrimers** have major role in **taste**

Target P2X3 to reduce cough; avoid P2X2/3 to maintain taste
Potency, Selectivity for Human hP2X3 vs. hP2X2/3

BLU-5937 is

10x more potent
>1000x more selective (vs P2X2/3)

than MK-7264 for the human P2X3 receptor

<table>
<thead>
<tr>
<th></th>
<th>BLU-5937</th>
<th>MK-7264</th>
</tr>
</thead>
<tbody>
<tr>
<td>hP2X3 (IC(_{50}))</td>
<td>Low nM</td>
<td>Mid nM</td>
</tr>
<tr>
<td>hP2X2/3 (IC(_{50}))</td>
<td>Mid µM</td>
<td>High nM</td>
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Fluorescent calcium flux assay, using Fluo-8 kit and 3 µM α,β Me AT, performed in HEK293 cells stably expressing P2X3 and P2X2/3; 12 concentrations of each compound tested.

BLU-5937: potential to inhibit cough with little/no taste disturbance
Preclinical Efficacy: Cough Response in Guinea Pig

BLU-5937 inhibits cough dose dependently and comparably to MK-7264

Cough Response Study

Treatments (control, BLU-5937, MK-7264) were administered orally (p.o.) 2 hours prior to tussive agent exposure: citric acid (0.1 M, aerosol) and histamine (0.6 mM, aerosol); n=6 animals per group

* p<0.05
Time Course Study (Guinea Pig Cough Model)

BLU-5937 inhibits cough comparably to MK-7264 and for a similar duration.

Treatments (control, BLU-5937, MK-7264; 30 mg/kg) were administered orally (p.o.) 2 hours prior to tussive agent exposure: citric acid (0.1 M, aerosol) and histamine (0.6 mM, aerosol); tussive agent exposure at 2, 4, 6, 8 and 12 hours for BLU-5937; at 2 and 8 hours for MK-7264; n=6 animals per group.

*p < 0.05
MK-7264 alters taste; BLU-5937 does not.

Effect of BLU-5937, MK-7264 on Taste in Rats

Two Bottle Rat Taste Study

Treatments (control, BLU-5937, MK-7264) were administered ip: animals were water-fasted overnight and presented with one bottle water and quinine (0.3mM) at $T_{max}$; volume of liquid consumed measured for 15 minutes; $n=10$ animals per group.

* $p < 0.05$ vs control
## Safety & ADME Profile Overview

<table>
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<tr>
<th>Safety Profile</th>
<th>ADME Profile</th>
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<tr>
<td>No safety findings of concern</td>
<td>Projected BID dosing</td>
</tr>
<tr>
<td>• Good safety margin in 7 day toxicity studies (rat &amp; dog)</td>
<td>• Good oral bioavailability</td>
</tr>
<tr>
<td>• No genotoxicity</td>
<td>• Elimination through metabolism</td>
</tr>
<tr>
<td>• Highly selective without off-target effect</td>
<td>• No drug interaction anticipated</td>
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<td></td>
<td>• Very low brain permeability</td>
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Phase 1 Study Design

Key Objectives

Assess Safety

Assess Tolerability Including Taste Effect

Measure Drug Plasma Levels for Phase 2 Dosing

Single Ascending Dose
n=48 healthy adult subjects
5 cohorts of 8 subjects administered single dose
1 cohort of 8 subjects to assess taste effect

Multiple Ascending Dose
n=24 healthy adult subjects
3 cohorts of 8 subjects administered multiple dose BID for 7 days

Traditional design; assess safety, tolerability (including taste), drug levels
Phase 2 Proof of Concept Study Design

- N=36 unexplained/refractory chronic cough patients; >1 year coughing
- 6 sites in UK and 2 sites in US
- 4 dose levels escalated at 4-day intervals
- Endpoint: reduction in frequency of cough (cough recorder)
- Safety and tolerability assessment, including taste effect

Similar design to Afferent/Merck Phase 2 proof of concept
## Development Milestones

<table>
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<tr>
<th>Q2 2018</th>
<th>Q3 2018</th>
<th>2019</th>
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<tbody>
<tr>
<td>File Clinical Trial Application</td>
<td>Start Phase 1</td>
<td>Start Phase 2</td>
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<tr>
<td>Safety margins</td>
<td>Effect on taste</td>
<td>Effect on cough and taste</td>
</tr>
<tr>
<td>Starting dose for Phase 1</td>
<td>Safety/tolerability</td>
<td>Dose selection for Phase 3</td>
</tr>
<tr>
<td></td>
<td>Dose selection for Phase 2</td>
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## Summary – BLU-5937

<table>
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<th>In vitro</th>
<th>Animal</th>
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<tr>
<td>More potent and selective P2X3 inhibitor versus leading P2X3 antagonist</td>
<td>Cough: comparable efficacy and duration vs. leading P2X3 antagonist</td>
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<td>Taste: no taste effect observed</td>
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### Phase 1 (2018)
- Taste effect data in humans

### Phase 2 (2019)
- Robust and efficient design

Strong and differentiated P2X3 drug candidate profile with efficient path to data