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Introduction & Agenda

Roberto Bellini
President & CEO
BELLUS Health
I. Introduction & Agenda
Roberto Bellini
President & CEO
BELLUS Health

II. Review of Chronic Cough and Potential Treatments
Prof. Jacky A. Smith, MB, ChB, FRCP, PhD
University of Manchester

III. BLU-5937, A Highly Selective P2X3 Antagonist for Chronic Cough – Preclinical & Phase 1
Dr. Denis Garceau
Vice President, Drug Development
BELLUS Health

IV. BLU-5937 – Phase 2 Study
Prof Jacky A. Smith MB, ChB, FRCP, PhD
University of Manchester

V. Commercial Considerations
Darren Eskow
Managing Director
Bluestar Bioadvisors

VI. P2X3 Platform Potential
Dr. Denis Garceau
Vice President, Drug Development
BELLUS Health

VII. Summary and Q&A
Review of Chronic Cough and Potential Treatments

Prof. Jacky A. Smith, MB, ChB, FRCP, PhD

University of Manchester
Chronic Cough Overview

- Chronic Cough: Lasts > 8 weeks
- Patient characteristics:
  - Average age: Mid 50s - Early 60s
  - More prevalent in women (~65%)
- Chronic cough may be associated with:
  - Pulmonary diseases (e.g. asthma, COPD, bronchiectasis, IPF, lung cancer)
  - Extra-pulmonary disorders (e.g. allergic rhinitis, gastroesophageal reflux)
  - Use of some drugs (e.g. ACE inhibitors)
  - No specific causes (unexplained cough; idiopathic)
- Current standard of care is to treat the underlying disease
The Refractory or Unexplained Chronic Cough Diagnostic Pathway

- Chronic Cough Patient
  - Chronic Cough with Associated Medical Conditions (e.g. UACS, Asthma, GERD)
    - "Refractory" Chronic Cough
      - Patients who are considered appropriate for treatment with a specific antitussive therapy

- Unexplained Chronic Cough
Refractory/Unexplained Chronic Cough Takes Substantial Toll on Patients

<table>
<thead>
<tr>
<th>PHYSICAL</th>
<th>SOCIAL</th>
<th>PSYCHOSOCIAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue and Sleep</td>
<td>• Interference with lifestyle,</td>
<td>• Anxiety</td>
</tr>
<tr>
<td>Deprivation</td>
<td>work, and leisure</td>
<td>• Anger</td>
</tr>
<tr>
<td>Vomiting</td>
<td>• Difficulty conversing</td>
<td>• Depression</td>
</tr>
<tr>
<td>Incontinence</td>
<td>• Embarrassment of coughing in public</td>
<td>• Distress</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rib Fracture</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chronic cough requires a safe, effective therapy that is non-narcotic and non-sedating.

<table>
<thead>
<tr>
<th><strong>OPIOIDS</strong></th>
<th><strong>DEXTROMETHORPHAN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can be efficacious</td>
<td>• Key ingredient in OTC cough suppressants</td>
</tr>
<tr>
<td>• Limited use, due to side effects</td>
<td>• Limited efficacy</td>
</tr>
<tr>
<td>• Potential for addiction</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>BENZONATATE</strong></th>
<th><strong>GABAPENTIN /PREGABALIN</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Anesthetizes the stretch receptors in the lungs</td>
<td>• Neuromodulators with variable efficacy and significant CNS side effects</td>
</tr>
<tr>
<td>• Temporary relief</td>
<td></td>
</tr>
<tr>
<td>• Potential serious side effects if capsule is broken</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>SPEECH THERAPY</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Has shown some efficacy, especially in combination with pharmacotherapy</td>
</tr>
</tbody>
</table>
Cough Hypersensitivity & The Role of P2X3 in Refractory or Unexplained Chronic Cough

P2X3 is a rational target to treat cough hypersensitivity in refractory/unexplained chronic cough

Cough Hypersensitivity

- Exaggerated sensation of the urge to cough, reflecting a disorder of the primary sensory neurons that innervate the airways and lung
- Cough is triggered by innocuous stimuli, such as perfume, cold air, exercise, stress, laughing, or talking; referred to as allotussia

Role of P2X3 Receptors

- ATP gated ion channels expressed in C-fiber neurons in the upper airways
- ATP released from damaged or inflamed tissues in the airways acts on P2X3 receptors triggering a feeling of irritation, causing the urge to cough

Kwong et al 2008 AJP Lung cell Mol Physiol 295 L858-65
P2X3 Receptor: Clinically Validated Target

MK-7264 Phase 2b Study (257 patients; 12 weeks)

MK-7264 showed reduction in awake cough frequency of 57% vs baseline and 37% vs placebo at 50mg dose

<table>
<thead>
<tr>
<th>MK-7264 Dose Levels</th>
<th>Estimated % Change (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.5 mg</td>
<td>-22 (-41.8, 4.6)</td>
<td>0.0971</td>
</tr>
<tr>
<td>20 mg</td>
<td>-22.2 (-42, 4.3)</td>
<td>0.0928</td>
</tr>
<tr>
<td>50 mg</td>
<td>-37 (-53.3, -14.9)</td>
<td>0.0027</td>
</tr>
</tbody>
</table>

Merck & Co., MK-7264 in Chronic Cough: Update on Clinical Development Programme; 10th International Symposium on Cough; June 2018
MK-7264 Phase 2b: Side Effect Profile

P2X3 is safe and well-tolerated, except for taste effect

Most Frequent Adverse Events (≥ 5%)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>7.5 mg BID MK-7264 (n=63)</th>
<th>20 mg BID MK-7264 (n=63)</th>
<th>50 mg BID MK-7264 (n=63)</th>
<th>Total MK-7264 (n=189)</th>
<th>Placebo (n=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>6 (9.5%)</td>
<td>21 (33.3%)</td>
<td>30 (47.6%)</td>
<td>57 (30.2%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Hypogeusia</td>
<td>0</td>
<td>11 (17.5%)</td>
<td>15 (23.8%)</td>
<td>26 (13.8%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (6.3%)</td>
<td>12 (19.0%)</td>
<td>4 (6.3%)</td>
<td>20 (10.6%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>5 (7.9%)</td>
<td>9 (14.3%)</td>
<td>6 (9.5%)</td>
<td>20 (10.6%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Ageusia</td>
<td>0</td>
<td>3 (4.8%)</td>
<td>13 (20.6%)</td>
<td>16 (8.5%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Paraesthesia Oral</td>
<td>4 (6.3%)</td>
<td>5 (7.9%)</td>
<td>4 (6.3%)</td>
<td>13 (6.9%)</td>
<td>5 (7.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (3.2%)</td>
<td>5 (7.9%)</td>
<td>5 (7.9%)</td>
<td>12 (6.3%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Hypoaesthesia Oral</td>
<td>2 (3.2%)</td>
<td>4 (6.3%)</td>
<td>5 (7.9%)</td>
<td>11 (5.8%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>4 (6.3%)</td>
<td>6 (9.5%)</td>
<td>10 (5.3%)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3 (4.8%)</td>
<td>5 (7.9%)</td>
<td>2 (3.2%)</td>
<td>10 (5.3%)</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>2 (3.2%)</td>
<td>3 (4.8%)</td>
<td>3 (4.8%)</td>
<td>8 (4.2%)</td>
<td>6 (9.5%)</td>
</tr>
</tbody>
</table>

12-Week study; N=257

- P2X3 class effects include taste effect, numbness, and nausea

Merck & Co., Presentation of gefapixant Phase IIb data; American Thoracic Society; May 2017
Adverse Events

- 80% of patients reported taste events at 50mg
- 40% reported taste events as very/extremely bothersome
- 10% of patients dropped out due to taste effect
- Taste-related adverse effects are persistent over time, and are reversible upon treatment cessation
Mechanisms in Development for Chronic Cough Have Faced Challenges

**TRP Modulators**
- All TRP modulators tested in-clinic to date have failed
- **GSK2798745** (GSK), a TRPV4 antagonist, terminated in Phase 2, following futility analysis

**NK1 Antagonists**
- **Serlopitant** (Menlo) development terminated due to lack of efficacy in Phase 2 study
- **Orvepitant** (NeRRe) missed its Phase 2 primary endpoint of cough frequency reduction; certain secondary endpoints positive

**nAChR Agonist**
- **ATA-101** (Attenua) Phase 2 study failed
P2X3 has Shown to be the Only Clinically Validated Treatment Approach to Date

P2X3 Antagonists

- Clinically validated pathway, with proven antitussive effect
- Merck’s **MK-7264** has two Phase 3 studies ongoing, with completion dates in mid-2020 and 1H 2021
- **BELLUS’ BLU-5937** had little to no taste effect in Phase 1; initiating Phase 2 study mid-2019
- Shionogi’s **S-600918** reported positive Phase 2 data in Japan-only single-dose trial; moving to dose ranging study
- Bayer’s **BAY1817080 & BAY1902607** Phase 2 studies expected to be completed in 2H 2019
MK-7264 Dose Escalation Studies

- Inhibition of P2X3 linked to efficacy
- Inhibition of P2X2/3 linked to taste effect

Crossover design; 4-day forced dose escalation; 2 cohorts from 7.5mg-50mg and 50mg-200mg
Shionogi’s Phase 2 Data Provides Clinical Validation for a Selective P2X3 Antagonist Approach in Reducing Cough

- S-600918 efficacy comparable to gefapixant
- Rate of taste effect not reported
- S-600918 selectivity has not been disclosed
  - Potentially similar to selectivity of only published Shionogi compound (173x selective for P2X3 vs. P2X2/3)¹
- Shionogi moving into dose-finding Phase 2 study

¹Tobinaga et al., 2017. Pyrrolinone derivatives as a new class of P2X3 receptor antagonists. Bioorganic & Medicinal Chemistry Letters

*Merck & Co., Presentation of gefapixant Phase IIb data; American Thoracic Society; May 2017
**Shionogi & Co., Ltd., Research and Development at Shionogi Presentation; March 2019
P2X3 Competitive Landscape

Best-in-class selectivity for P2X3, supports potential best-in-class profile

<table>
<thead>
<tr>
<th>Company</th>
<th>Candidate</th>
<th>Dosing</th>
<th>P2X3 vs. P2X2/3 Selectivity</th>
<th>Anti-Tussive Effect</th>
<th>Taste Interference</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellus Health</td>
<td>BLU-5937</td>
<td>50-100mg BID</td>
<td>~ 1500x</td>
<td>High</td>
<td>Low/None</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Merck</td>
<td>MK-7264</td>
<td>15mg BID</td>
<td>2-7x</td>
<td>High</td>
<td>High</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Bayer</td>
<td>BAY ’080 &amp; BAY ’607</td>
<td>45mg BID</td>
<td>25-125x*</td>
<td>High</td>
<td>Moderate/Low</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Shionogi</td>
<td>S-600918</td>
<td>BID</td>
<td>173x**</td>
<td>High</td>
<td>Moderate/Low</td>
<td>Phase 2^</td>
</tr>
</tbody>
</table>

* Bayer selectivity range of 419 P2X3 antagonists described in Bayer US patent 10,183,937 (may not be BAY1817080 or BAY1902607)
** Shionogi selectivity value presented in Tobinaga et al., 2017 for a representative, single, optimized P2X3 antagonist generated by Shionogi (may not be S-600918)
† Effect on taste and anti-tussive effect are company estimates based on animal data, clinical data, dose, human P2X3 potency, and human P2X3 vs. P2X2/3 selectivity
^ Phase II study conducted in Japan
BLU-5937, A Highly-Selective P2X3 Antagonist for Chronic Cough – Preclinical & Phase 1

Dr. Denis Garceau,
Vice President, Drug Development
BELLUS Health
**Targeting P2X3 to Treat Chronic Cough**

**Hypothesis:** Selective inhibition of P2X3 homotrimeric receptors would reduce cough, with little or no impact on taste perception.

**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
At doses that blocked P2X3 but not P2X2/3 receptors, BLU-5937 reduced cough with no taste effect.
Validated Efficacy Target—Clinical

Selective S-600918 has comparable efficacy to low selectivity MK-7264

Reduction in Cough Frequency

**MK-7264 Phase 2B**
(Dose Undisclosed)
- 57% Nominal
- 37%* Placebo Adjusted

*Merck & Co ATS Presentation, May 22, 2017; *p<0.01

**S-600918 Phase 2A**
(Dose Undisclosed)
- 53% Nominal
- 32%* Placebo Adjusted

*Research and Development at Shionogi Presentation, March 14 2019; **p=0.055
BLU-5937: Drug-Like Characteristics

EXCELLENT PHYSIO-CHEMICAL PROPERTIES

- Solubility
- Permeability

DOES NOT CROSS BLOOD-BRAIN BARRIER

- No adverse effect on general behavior, neurological function in rats
- Non-sedative

GOOD ORAL BIOAVAILABILITY (ACROSS NUMEROUS ANIMAL SPECIES)

- 48-80%

7-DAY, 28-DAY TOXICITY STUDIES (RAT AND DOG)

- High safety margin in preclinical toxicity studies
- Main toxicity target organ at high doses (≥ 300 mg/kg/day); GI tract
- Irritation of GI mucosa; emesis; reduction in weight gain

GOOD METABOLIC STABILITY IN HUMAN HEPATOCYTES OR LIVER MICROSONES

- BID dosing confirmed in Phase 1
- Eliminated primarily through hepatic metabolism
- Low potential of DDI
BLU-5937: Phase 1 Study Design

**Design:** A randomized, double-blind, placebo-controlled, escalating single dose followed by escalating multiple dose Phase 1 study conducted in 90 healthy adult subjects

**Objective:** To test the safety, tolerability, and pharmacokinetic profile of BLU-5937

---

**Single Ascending Dose (SAD)**
- N=60 healthy subjects
- 6 cohorts of 10 subjects (8 active; 2 placebo) administered single doses of 50mg to 1200mg
- Food effect tested at 200mg in one cohort

**Multiple Ascending Dose (MAD)**
- N=30 healthy subjects
- 3 cohorts of 10 subjects (8 active; 2 placebo) administered multiple doses of 100mg, 200mg, and 400mg BID for 7 days
BLU-5937: Excellent PK Profile in Healthy Subjects

Observations:
- BLU-5937 is rapidly absorbed ($T_{\text{max}} \sim 1\text{h}$)
- Systemic exposure increases dose-proportionally
- Plasma half-life of 4-9 hours supports BID dosing
- No significant effect of food on PK
- No significant systemic accumulation over 7 days
BLU-5937 Human Predicted Doses (50-100 mg BID)

BLU-5937 predicted dose expected to be 50-100mg BID, based on achieving at least 5x drug free plasma to IC50 ratio

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Plasma concentration at maximal efficacy (ng/ml)</th>
<th>Plasma concentration (nM)</th>
<th>Free plasma concentration (nM)</th>
<th>IC50 for P2X3 (nM)</th>
<th>Ratio free plasma concentration / IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLU-5937</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure - Guinea Pig Cough Model</td>
<td>30 mg/kg</td>
<td>2031</td>
<td>4400</td>
<td>700</td>
<td>126</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>MK-7264</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure in Phase 2b</td>
<td>50 mg</td>
<td>300*</td>
<td>850</td>
<td>383</td>
<td>76</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>BLU-5937</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure (Cave) in Phase 1</td>
<td>50 mg</td>
<td>408</td>
<td>890</td>
<td>125</td>
<td>25</td>
<td>5.0</td>
</tr>
</tbody>
</table>

BLU-5937 free fraction in humans (14%); free fraction in guinea pig (16%)
MK-7264 MW (353); free fraction in human (45%), free fraction in guinea pig (68.6%)

Ford A. The 8th Annual Pain & Migraine Therapeutics Summit; 2014
Merck & Co., Presentation of gefapixant Phase IIb data; American Thoracic Society; May 2017
BLU-5937: Safe & Well-Tolerated

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

<table>
<thead>
<tr>
<th>AEs N (%)</th>
<th>Placebo (n=18)</th>
<th>50mg (n=8)</th>
<th>100mg (n=16)</th>
<th>200mg (n=16)</th>
<th>400mg (n=16)</th>
<th>800mg (n=8)</th>
<th>1200mg (n=8)</th>
<th>Total BLU-5937 (n=72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taste Alteration</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>6 (38%)</td>
<td>5 (63%)</td>
<td>2 (25%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Hypoaesthesia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (19%)</td>
<td>2 (13%)</td>
<td>3 (38%)</td>
<td>0 (0%)</td>
<td>8 (11%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>1 (13%)</td>
<td>1 (13%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>1 (6%)</td>
<td>2 (25%)</td>
<td>2 (25%)</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>1 (13%)</td>
<td>0 (0%)</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>

- 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, nausea
- One subject had mild liver enzyme elevation (400mg BID) that normalized at follow up; not associated with increased bilirubin
Low Incidence of Taste Effect at Predicted Therapeutic Doses

Incidence of Taste AEs (All Cohorts SAD + MAD)

<table>
<thead>
<tr>
<th></th>
<th>50 mg (n=8)</th>
<th>100 mg (n=16)</th>
<th>200 mg (n=16)</th>
<th>400 mg (n=16)</th>
<th>800 mg (n=8)</th>
<th>1200 mg (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysgeusia</td>
<td>0 (0%)</td>
<td>1 (6.3%)</td>
<td>0 (0%)</td>
<td>6 (37.5%)</td>
<td>5 (62.5%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Hypogeusia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (6.25%)</td>
<td>1 (12.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ageusia</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

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 out of 24 subjects (4.2%) reported taste effect at the anticipated therapeutic doses (50-100mg)
- 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)
Best-in-Class Taste Tolerability Profile

| Incidence and Severity of Taste Effect AEs at Estimated Comparative Therapeutic Doses |
|-----------------------------------------------|-----------------------------------------------|
| **Dose(s)** | **BLU-5937 (50-100mg) (n=24)** | **Gefapixant\(^1\) (50mg) (n=57)** |
| 50 and 100mg single dose, and 7 day BID cohorts | 50mg BID arm for 12 weeks |
| **Subjects** | Healthy Volunteers | Refractory Chronic Cough |
| **Taste Alteration** | <5% | 48% |
| **Partial Taste Loss** | 0% | 24% |
| **Complete Taste Loss** | 0% | 20% |
| **All Taste AEs** | <5% | 81% |

\(^1\)Merck & Co Presentation of gefapixant Phase 2b data at American Thoracic Society 2017

\(^2\)A. Morice et al, The Effect of MK-7264, a P2X3 antagonist, on Cough Reflex Sensitivity in a Randomized Crossover Trial of Healthy and Chronic Cough Subjects
Conclusions

BLU-5937 has excellent PK and safety/tolerability profile

- Linear PK, twice-daily dosing, no food interaction
- Only one mild, transient, and sporadic taste alteration at predicted therapeutic doses

These data represent the first evidence that a highly selective P2X3 antagonist is associated with an improved taste safety profile in humans.

Results support advancing to Phase 2
RELIEF: A Randomized, Double-Blind, Placebo-Controlled, Crossover, Dose Escalation Study of BLU-5937 in Subjects with Unexplained or Refractory Chronic Cough—BLU-5937 Phase 2 Study

Prof. Jacky A. Smith, MB, ChB, FRCP, PhD

University of Manchester
Clinical Studies in Chronic Cough

Recent learnings in clinical studies have provided a clear path for development and approval of chronic cough drugs

### Crossover Design
- Efficient for Phase 2 proof-of-concept
- Allows for multiple dose assessment in limited number of patients
- Results confirmed in longer-term study

### Endpoints
- Reduction in awake cough frequency, as measured by cough recorder
- Good correlation between cough frequency and patient reported outcomes
- Potential for placebo effect

### Regulatory
- At least two large Phase 3 studies required for approval, including important safety database to support chronic use
- Primary efficacy endpoint is 24-hour cough frequency reduction using validated cough recorder
Vitalograph’s Vitalojak Cough Recorder

- CE mark
- FDA 510k registration
- 99.9% sensitivity

Vitalograph’s Vitalojak is a validated cough recorder accepted by FDA
Phase 2 Study: Overview of Study Design

- Randomized, double-blind, placebo-controlled and 2-periods crossover design
- ~65 unexplained or refractory chronic cough patients
- 12 trial sites in UK and USA
- 4 dose levels with forced escalation at 4-day intervals (25/50/100/200mg, twice daily)
- Awake and 24-hour cough recording at end of each dose intervals
- 2-week screening period and 2-week follow-up with cough recordings
Phase 2 Study: Experienced Sites

- 12 sites in total; 9 UK, 3 US
- All sites experienced with conducting chronic cough studies, including at least one P2X3 antagonist
- Many sites are chronic cough centers of excellence with access to significant basin of patients
- Relatively few competing studies on-going

San Jose, California
San Antonio, Texas
Largo, Florida
Belfast
Manchester
Cottingham
Leicester
North Shields
Watford
Stevenage
London (2)
# Phase 2 Study: Main Entry Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Prohibited Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Unexplained or refractory chronic cough for $\geq$ 1 year</td>
<td>- Diagnosis of COPD, bronchiectasis, IPF</td>
<td>- Anti-cough medications; (dextrometorphan, gabapentin, pregabalin, opioids)</td>
</tr>
<tr>
<td>- Cough count $\geq$ 10 coughs/hour, at screening</td>
<td>- Current/former smokers (within 6 months)</td>
<td>- Long-term oral steroids (prednisone)</td>
</tr>
<tr>
<td>- Score $\geq$ 40 on cough severity VAS at screening</td>
<td>- FEV1/FVC $&lt; 60%$</td>
<td>- Medications to treat underlying disease/allergies (inhaled steroids, antihistamines)</td>
</tr>
<tr>
<td></td>
<td>- History of upper respiratory tract infection or recent significant change in pulmonary status within 4 weeks of baseline</td>
<td>must be on stable doses for at least 8 weeks prior to screening visit</td>
</tr>
</tbody>
</table>
Phase 2 Study: Efficacy & Safety Endpoints

**Primary Efficacy Endpoint:**
- Change from baseline in awake cough frequency (cough recorder) at end of each dose level

**Principal Secondary Efficacy Endpoints:**
- Change from baseline in:
  - 24-hour cough frequency at end of each dose level
  - Cough severity, as measured with VAS at the end of each dose level
  - Leicester cough questionnaire total score at the end of each treatment period
- Global Rating of Change Scale at the end of each dose level
- Percent of subjects with ≥ 30, 50, 75% reduction in awake cough count from baseline at end of each dose level

**Safety Endpoints:**
- AEs; vital signs; ECG; clinical laboratory; BLU-5937 plasma levels
- Spontaneous taste disturbance AEs
Timeline

IND/CTA FILING

- IND cleared with US FDA
- Clinical Trial Application cleared with UK MHRA

PHASE 2 START

- US sites have started recruiting
- UK sites start recruiting end-July/early-August
- First patient dosed end-July/August

PHASE 2 DATA

- Topline safety and efficacy data readout

Q1-Q2 2019

July/August 2019

Mid-2020
Commercial Considerations:

Darren Eskow
Managing Director
Bluestar Bioadvisors
Prevalence of Refractory/Idiopathic Chronic Cough

Addressable Patient Population

US Adult Population
263M

26.3M or 10%
Chronic Cough Patients

2.6M
Primary addressable patients
(Idiopathic/Treatment refractory
> 1 year)

9.1M
Secondary addressable patients
(Treatment Refractory
> 8 weeks < 1 year)
### BLU-5937 Comparable Price Analogs

<table>
<thead>
<tr>
<th>Indication</th>
<th>Addressable US Patient Population</th>
<th>Market Dynamics</th>
<th>2019 WACC/mo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Linzess</strong> (linvicol) capsules</td>
<td>Chronic idiopathic constipation</td>
<td>Genericized</td>
<td>$424</td>
</tr>
<tr>
<td></td>
<td>35M</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>amitiza</strong> lubiprostone</td>
<td>IBS with constipation</td>
<td>Genericized</td>
<td>$371</td>
</tr>
<tr>
<td></td>
<td>4M</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADVAIR DISKUS</strong></td>
<td>Adult asthma and Adult COPD</td>
<td>Highly competitive, several generics</td>
<td>$394</td>
</tr>
<tr>
<td></td>
<td>18.4M</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12M</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Aptiom</strong></td>
<td>Partial onset seizures</td>
<td>Highly competitive</td>
<td>$968</td>
</tr>
<tr>
<td></td>
<td>1M</td>
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</tr>
</tbody>
</table>
Primary Care Physician: Initial Physical Exam and Clinical History

- **Persistent cough not responsive to OTC cough suppressants**
  - **PCP**
  - **Initial point of care for most patients**

- **Treat Empirically**
  - Clinical history and physical exam suggest underlying diagnosis

- **Chest X-ray**
  - History and physical exam do not strongly suggest cause

- **Allergy Testing**

- **Remove Exogenous Triggers**
  - Allergic/environmental irritants, switch medicines

- **Refractory or Idiopathic**
  - Referral

---

**Specialist Workup**

- **Allergist/Immunologist**
  - Pulmonary Function Test (PFT)
  - Spirometry
  - Nasal swabs/culture
  - Methacholine challenge
  - Allergy skin testing

- **Pulmonologist**
  - PFT
  - Bronchoscopy
  - CT scans - lung

- **ENT**
  - Sinus imaging/scoping
  - Laryngoscopy
  - CT scans - sinus cavity

- **Gastroenterologist**
  - Endoscopy
  - Manometry
P2X3 Platform Potential

Dr. Denis Garceau,
Vice President, Drug Development
BELLUS Health
Potential for Broad Applicability

Inhibition of P2X3 receptors has therapeutic potential in a number of other indications

OTHER INDICATIONS LINKED TO P2X3 HYPERSENSITIZATION

- Hypersensitive cough
- Migraine
- Hypertension
- Bronchoconstriction
- Sleep apnea
- IBS
- Pruritus
- Bladder pain
- Endometriosis pain
- Neuropathic pain
Potential for Pipeline in a Product

Recent P2X3 Studies and Indications Being Pursued

**Cough Indications**

- **ACUTE COUGH**
  - Phase II study conducted by Merck

- **CHRONIC COUGH**
  - Programs on-going at Merck, Bellus Health, Shionogi and Bayer

- **IPF COUGH**
  - Phase II study conducted by Merck

**Other Indications**

- **ENDOMETRIOSIS PAIN**
  - Phase II study started by Merck

- **OBSTRUCTIVE SLEEP APNEA**
  - Phase II study started by Merck

- **UNDISCLOSED INDICATION**
  - Bellus preclinical studies ongoing
Summary and Q&A