

Assessment of the Market Potential for BLU-5937 in Chronic Cough

Presentation Prepared for



Bellus
HEALTH

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Conducted in-depth interviews with community PCPs and specialists as well as KOLs treating chronic cough

Research Approach and Methodology

Key Stakeholders	U.S. Interview Targets
PCPs	5
Allergists/Immunologists	7
Pulmonologists	2
ENTs	1
Gastroenterologist	1
3 Specialist KOL	3
2 Cough Clinic KOL	2

Secondary Research
<ul style="list-style-type: none"> • Professional, peer-reviewed journals (representative) <ul style="list-style-type: none"> - Chest - Lancet - NEJM - The American journal of gastroenterology - Annals of Allergy, Asthma & Immunology • Databases <ul style="list-style-type: none"> - UptoDate - ADIS - Redbook - ThomsonOne Financials - IMS Health

Insights used the following product profile to test the potential for BLU-5937 in the chronic cough market

Indication	Refractory chronic cough (cough lasting > 1 year)			
Overall Rationale	<ul style="list-style-type: none"> P2X3 receptors are expressed by airway vagal afferent nerves and contribute to the hypersensitization of sensory neurons. Targeting P2X3 in chronic cough has been validated based on a demonstration of efficacy in clinical trials by a competitor program; however, the competitor has been associated with high rates of taste disturbances Product X, which is more selective for P2X3 (as compared P2X2/3) has the potential to provide a treatment that is comparable in efficacy to the first-in-class competitor P2X3 antagonist, but with reduced impact on taste disturbance 			
MOA	P2X3 antagonist			
Treatment Approach	Chronic use in patients as a monotherapy			
Dosing	BID, administered orally			
Preclinical Data To Date	<i>Head to head data against first in class P2X3 competitor</i>			<i>Safety Data</i>
	<u>Reduced taste disturbance</u> <ul style="list-style-type: none"> Lower consumption of quinine vs. water consumed by rats 	<u>Comparable efficacy:</u> <ul style="list-style-type: none"> Dose-dependent cough frequency reduction in guinea pig cough model Antitussive Effect Correlates with in vitro IC50 at P2X3, not at P2X2/3 	<u>Superior Potency and Selectivity</u> <ul style="list-style-type: none"> 1 log more potent than the P2X3 competitor 3 log more selective for P2X3 (cough receptor) vs. P2X2/3 (taste receptor) in human cells 	<ul style="list-style-type: none"> No genotoxicity No significant effect on hERG test No clinical safety findings of concern
Anticipated Clinical Efficacy	<i>Comparable to P2X3 competitor, which has demonstrated efficacy in phase IIb clinical studies (in 253 patients), as shown below:</i> <ul style="list-style-type: none"> Primary endpoint: significant reduction in awake cough frequency (coughs/hr) after 12 weeks treatment <ul style="list-style-type: none"> 84% reduction in awake cough frequency (coughs/hour) vs. baseline in P2X3 group 37% reduction (p < 0.003) of awake cough frequency (coughs/hour) in P2X3 group vs. placebo Secondary endpoint: significant improvement in LS-mean improvement in cough severity (VAS) after 12 weeks treatment <ul style="list-style-type: none"> 33.3% reduction in cough severity vs. baseline in P2X3 group 15.5% LS-mean improvement (p<0.003) in cough severity (VAS) in P2X3 group vs. placebo 			
Anticipated Clinical Safety (AEs)	<i>Superior to P2X3 competitor, benchmark data for which is shown below</i> <ul style="list-style-type: none"> ~80% of patients reported taste alteration ~20% of patients reported complete taste loss ~40% of patients reported very/extremely bothersome taste effects ~10% discontinuation due to AEs, most of which are related to taste disturbance 			

Physicians are enthusiastic about BLU-5937 due to its ability to address unmet needs in the chronic cough population; physicians reacted positively to a variety of BLU-5937's attributes

Overall Reaction

Physicians responded very positively to BLU-5937 due to its ability to treat idiopathic and refractory patients, a significantly underserved population, the potential superior tolerability profile to MK-7264, and the novel mechanism enabling use across all chronic cough patients

Patient Segments

BLU-5937 can be used in multiple settings as physicians seek to find a diagnosis for patients and for idiopathic and treatment refractory patients near term; BLU-5937 has the potential to expand use of symptomatic therapies, such as in the acute setting

Efficacy

BLU-5937's target efficacy is considered significantly superior to current cough treatments today, especially as a monotherapy; physicians are interested in the ability for the drug to reduce the number of other therapies needed and their associated costs required to manage chronic cough

Safety/Tolerability

Physicians had a negative reaction to the taste disturbance profile of MK-7264, particularly for patients that would rely on this chronically; a few noted that some patients are severe enough that taste disturbance isn't as much of an issue

Key Prescribers

While physicians believe that PCPs would be the biggest prescribers of BLU-5937 in terms of volume, physicians felt that allergists/immunologists and pulmonologists would be the early adopters to target since they manage more refractory patients

Drivers/Hurdles

The validation of the class with the approval of MK-7264 and clinically proven superiority in taste disturbance are key drivers for BLU-5937

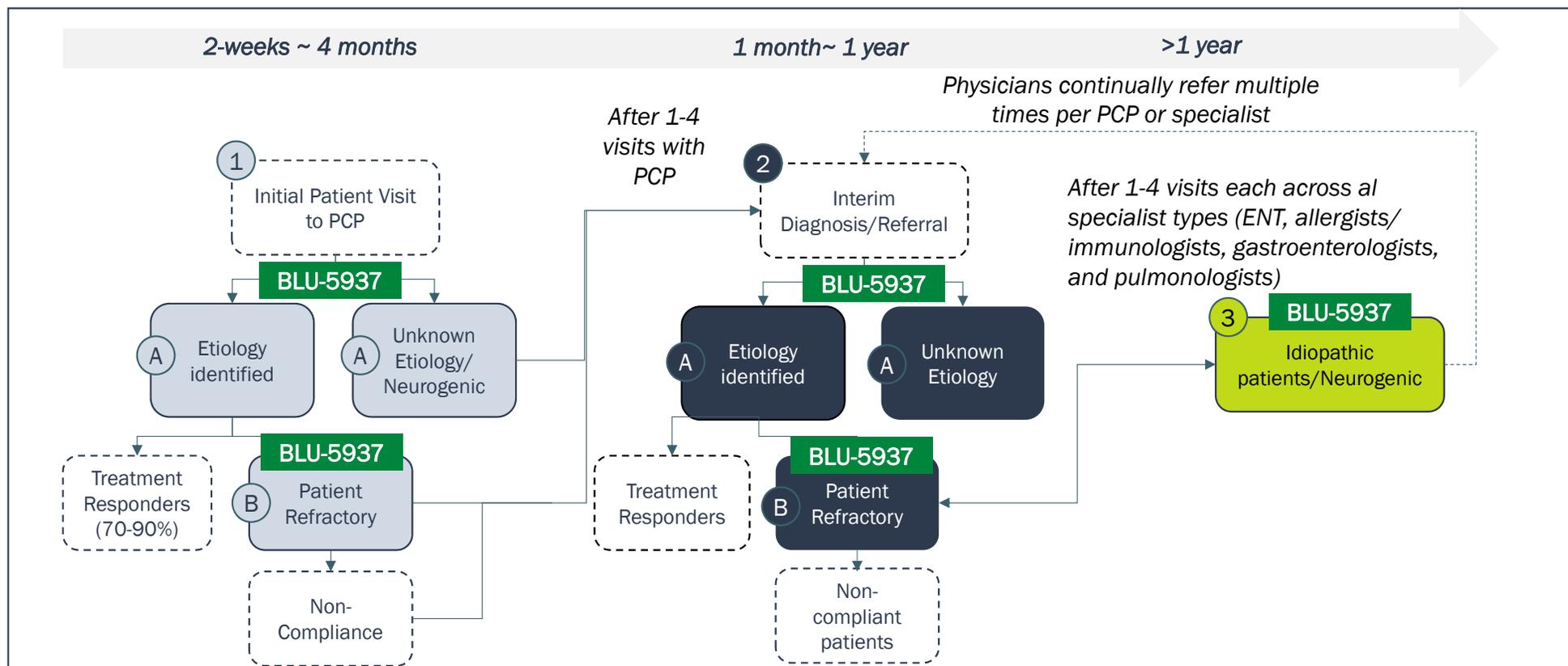
Most physicians responded very positively to BLU-5937 due to its ability to address an unmet need in the chronic cough space and as an agent with a superior tolerability profile to MK-7264 that can address multiple types of coughs

Overall Reaction to Product Profile

<p>Overall ability to meet unmet need, especially for idiopathic patients</p>	<p>All respondents reacted positively to the profile because of its potential to treat idiopathic patients, which remains the most underserved population with the fewest treatment options available.</p> <p><i>“If it’s effective and safe, this could have a dramatic effect on the idiopathic patient population” –Allergist/Immunologist</i></p> <p><i>“There is a clinical need for a product of this sort. If it really works, this would be great. It would definitely fill a need, and I would implement this product in my practice if it were approved. I would certainly use it in a certain group of patients, i.e. patients without an identifiable cause.” – Allergist/Immunologist</i></p>
<p>Ability to address multiple types of coughs</p>	<p>Interviewees were enthusiastic about the wide range of potential patients that this drug could be used in, however one cough clinic KOL noted its limitation as a peripherally acting agent</p> <p><i>“P2X3 targets the common denominator that remains after exogenous triggers are removed. It’s irrelevant of whether the cough is due to acid reflux, post-nasal drip, bronchitis, allergy.”–Gastroenterologist</i></p> <p><i>“According to data, I believe 30% of patients won’t respond. That’s not surprising since the dug is peripheral, so it will only work in patients whose cough is being triggered by some ATP-dependent pathway” –Cough Clinic KOL</i></p>
<p>Strongly encouraged by having a new option with a novel mechanism</p>	<p>Physicians were enthusiastic about having another option for chronic cough, especially since outside of P2X3 agents, the majority of respondents did not know of any emerging drugs in development</p> <p><i>“I like the idea of increased receptor selectivity so that it decreases side effects, and if they can achieve similar efficacy [to MK-7264], it sounds pretty cool. This is totally different compared to treatments today” – PCP</i></p> <p><i>“We do need a highly selective drug targeting P2X3 rather than P2X2/P2X3. The current drug in development produces a terrible sense of taste problem.” - Gastroenterologist</i></p>

According to physicians, there is high potential for BLU-5937 to be used throughout a patient's journey across multiple specialists and patient segments

BLU-5937 Target Segments



* Rates based on interview feedback and may change upon additional secondary research and additional primary feedback

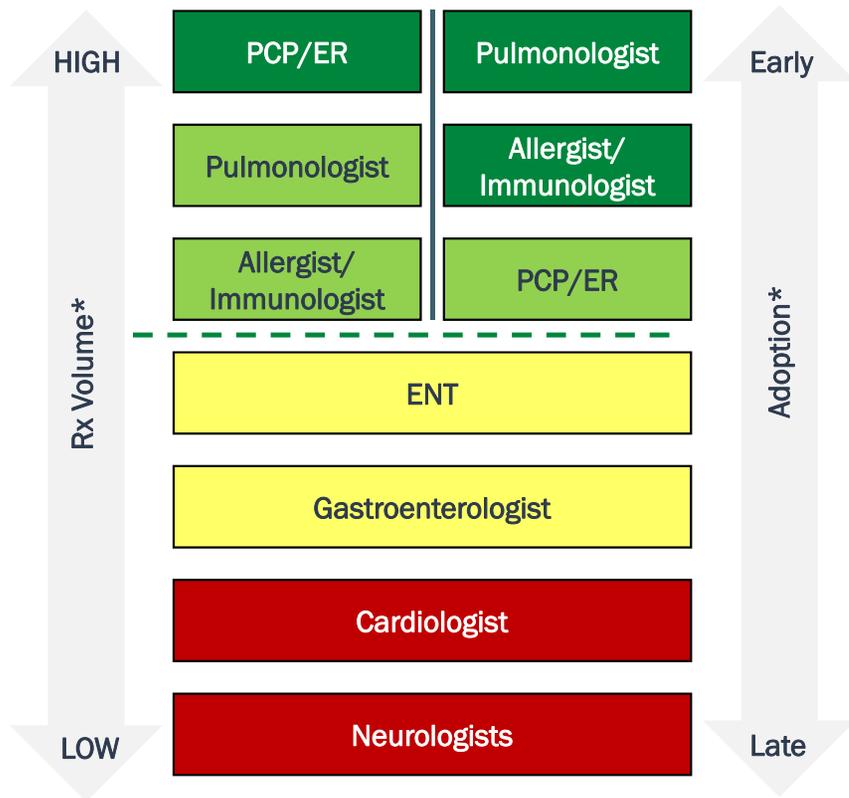
Almost all the physicians were concerned with the taste disturbance of MK-7264, especially if they persist long term throughout treatment; physicians desire a drastically lower taste disturbance profile especially for the rate of complete taste loss

Taste disturbance (MK-7264 endpoints serves as proxy for BLU-5937 potential performance)

TPP ENDPOINT	KEY TAKEAWAYS	PHYSICIAN FEEDBACK
20% Complete Taste Loss	<ul style="list-style-type: none"> The 20% complete taste loss was the most concerning AE, especially if product is used long term 	<ul style="list-style-type: none"> "That's a problem that 1/5 patients will lose taste... the most acceptable is 0%. No patients should experience loss of taste. -Gastroenterologist
40% bothersome taste effects	<ul style="list-style-type: none"> The 40% rate for those with bothersome effects was also considered disturbing 	<ul style="list-style-type: none"> "20% report complete taste loss, talk about compliance issues"- Allergist/Immunologist "Assuming it is reversible, and that if they stop and taste normally, then I think it's a hard question, maybe 10%. If it wasn't reversible, my answer would go way down." -PCP
80% taste alteration	<ul style="list-style-type: none"> Some respondents were very concerned that majority of patients would be affected 	<ul style="list-style-type: none"> "In real life, that 10% will be 30%...patient gets paid for a visit and are therefore motivated to take the medicine....you'll put up with the drug when in real life you would actually discontinue it - Allergist/Immunologist
10% discontinuation rate	<ul style="list-style-type: none"> Some viewed that discontinuation would be higher in clinical practice Others found that while majority of patients get taste alterations, the discontinuation rate suggest that patients tolerate it Few are willing to prescribe if effects are temporary, but only for severe patients 	<ul style="list-style-type: none"> "I'd want to reduce taste alterations to <10%. I want that in writing so that any incidents are on the pharmaceutical company not me: -ENT "I wouldn't mind this profile in really sick patients who are willing to try anything to treat their coughs. However, for less severe cases I'd recommend other drugs such as Tessalon" - Allergist/Immunologist "10% discontinuation -this gives me a sense of how tolerable this is for patients. Those patients on it must be very sick and willing to tolerate this, but every patient has a different threshold so you need a significant reduction in that side effect." -PCP

Interviewees believe that PCPs are the key prescribers in terms of volume; however, multiple interviewees feel that PCPs will adopt later than specialists who will want to observe specialists' experience in treating more refractory patients

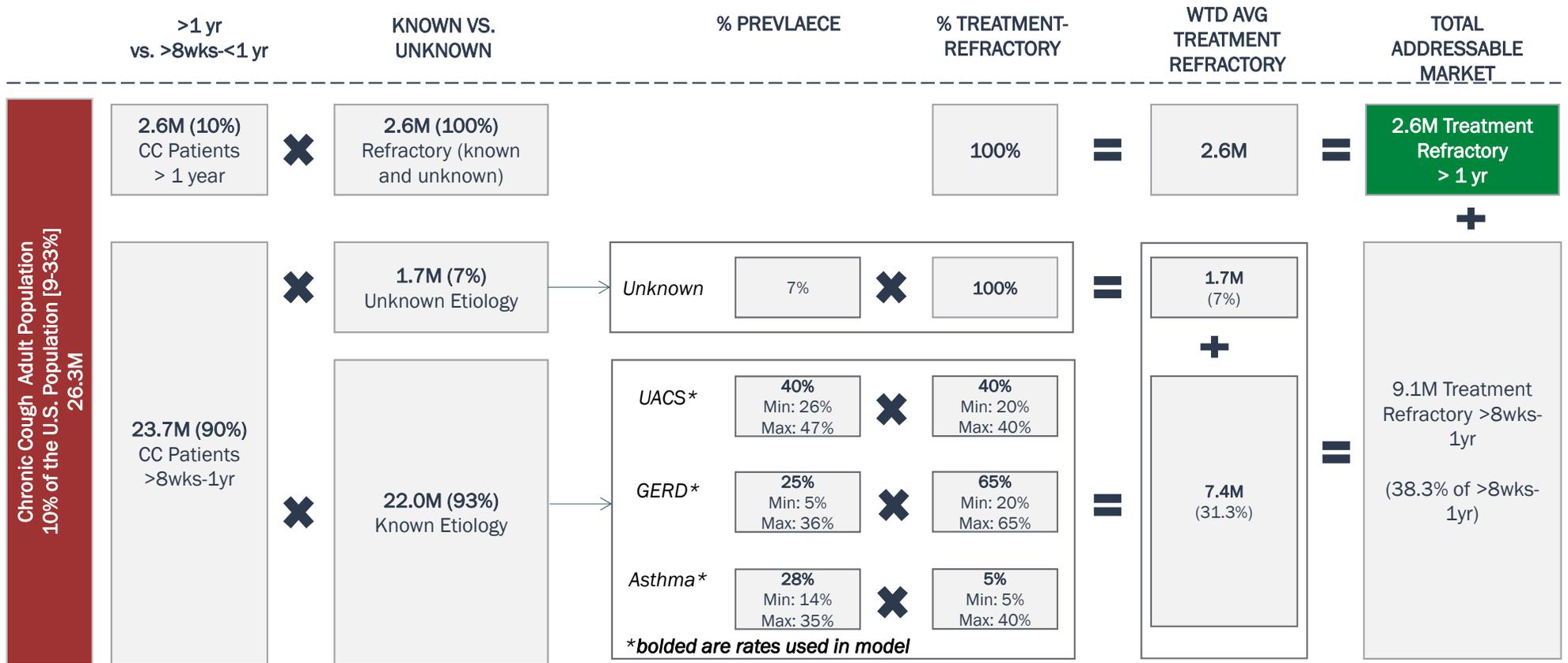
Expected Key Prescribers and Adopters of BLU-5937



	PRESCRIPTION VOLUME	ADOPTION PATTERNS
PCP	<ul style="list-style-type: none"> Initial point of care for most chronic cough patients Largest prescriber of symptomatic relief medicines 	<ul style="list-style-type: none"> Tend to look to see success rates experienced by specialists Adherent to guidelines and label
Pulmonologist	<ul style="list-style-type: none"> Most common referrals from PCPs Actively involved in medical management of patients 	<ul style="list-style-type: none"> First specialists to target are those that treat chronic cough of >1 year All allergy/immunologists considered themselves first adopters since willing to be more aggressive in treatment Specialists more willing to adopt novel agents in practice than PCPs
ENT	<ul style="list-style-type: none"> Not as extensively involved in the medical management of patients –primarily scoping/imaging and return patient back to referring physician 	<ul style="list-style-type: none"> Not as concerned with symptomatic relief treatments masking symptoms as medicine do not interfere with the diagnostic workup procedures
Gastro-enterologist		
Cardiologist	<ul style="list-style-type: none"> Likely won't prescribe – they are referred only if patients need to switch medicines (e.g. ACE inhibitors) 	
Neurologists	<ul style="list-style-type: none"> Likely won't prescribe—prescribe more for psychosomatic or neurogenic causes (e.g. anti-anxiety meds or speech therapy) 	
Cough Clinic Specialists	<ul style="list-style-type: none"> Would prescribe greatly, but likely to only see a minority of patients Relative volume depends on the label. Should they require patients to have prior authorization or step edits to ensure chronic refractory cough, cough clinic specialists would be more involved 	

Based on the MK-7264 inclusion criteria, the addressable market is 2.6M for idiopathic and treatment refractory patients who have had chronic cough >1yr; upside populations add ~9.1M comprising of CC patients 8wks-1 yr

Total Addressable Patient Segments



Pricing Comparables: Payers discussions and product analogs support pricing of \$300-600 per month

BLU-5937 Price Analogs

	Indication	Addressable US Patient Population	Market Dynamics	2016 WACC/mo
 <i>(linaclotide) capsules</i>	Chronic idiopathic constipation	35M	Genericized	\$319
 lubiprostone	IBS with constipation	4M	Genericized	\$330
	Adult asthma and Adult COPD	18.4M 12M	Highly competitive, several generics	\$289
 levamisole tablets	Partial onset seizures	1M	Highly competitive	\$570
BLU-5937	Chronic cough	2.6M	Highly competitive, several generics	\$300-600

BLU-5937 Market Assessment - Summary

- Interviews with physicians and KOLs, in addition to secondary research, revealed that the initial addressable chronic cough patient population in the US represents approximately 2.6 million patients
- Physicians interviewed were enthusiastic about the profile of BLU-5937
 - Ability to address unmet medical need
 - Superior tolerability to Merck's MK-7264
- Primary care physicians, allergists and pulmonologists will be the key prescribers for BLU-5937
- Discussions with payers and analog product analysis support pricing of \$300 - \$600 per month