Anti-IL25 Antibodies for Treatment of Asthma Exacerbations
Anti-IL-25 antibody - A potential new approach for treatment of exacerbations caused by viral infection in uncontrolled asthma patients

- Viral infection of the bronchial epithelium causes increased expression of the epithelial cytokine IL-25 which triggers the lung inflammation associated with asthma exacerbations
  - Cytokine production occurs in the context of the bronchial epithelial environment which controls the immune response
  - Other epithelial cytokines IL-33 and TSLP are not expressed in response to viral infection in the majority of uncontrolled asthma patients
  - Ex vivo studies conducted by Abeome in differentiated bronchial epithelial cells from healthy and asthmatic subjects support the unique role of IL-25 during viral infections

- ~32 million patients with uncontrolled asthma presents a significant market opportunity
  - No other anti-IL-25 mAb candidate is currently in development
  - Unique mechanism of action – viral induction of IL-25 which initiates type 2 immune response (asthma exacerbation)
  - Differentiation from other later-acting type-2 cytokines (IL-4, IL-5, IL-13) providing competitive advantage in projected $9B market
Asthma Market: Targeted by biologics manufacturers

Antibody products represent the majority of the projected market growth

Figure 1: Asthma sales in the US, Japan, and five major EU markets, by country ($m), 2015–24

- **Sales 2015 - 24:**
  - Min: 2015: $14,466m
  - Max: 2024: $21,999m

- **CAGR 2015 - 24:** 4.77%

- **Sales Change 2015 - 24:** $7,533m

Source: Datamonitor Healthcare
### BofA estimates a $9B market in uncontrolled asthma for antibodies to downstream Type-2 Cytokines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Company</th>
<th>Unrisk Peak Sales ($m)</th>
<th>Probability to Market</th>
<th>Risk Adjusted Peak Sales ($m)</th>
<th>Year of Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dupilumab</td>
<td>Anti-IL4/13</td>
<td>Sanofi/REGN</td>
<td>2,509</td>
<td>70%</td>
<td>1,756</td>
<td>2017</td>
</tr>
<tr>
<td>Benralizumab</td>
<td>Anti-IL5</td>
<td>AstraZeneca</td>
<td>1,500</td>
<td>70%</td>
<td>1,050</td>
<td>2017</td>
</tr>
<tr>
<td>“Nucala” Mepolizumab</td>
<td>Anti-IL5</td>
<td>GSK</td>
<td>2,635</td>
<td>95%</td>
<td>2,503</td>
<td>2016</td>
</tr>
<tr>
<td>Tralokinumab</td>
<td>Anti-IL13</td>
<td>AstraZeneca</td>
<td>500</td>
<td>70%</td>
<td>350</td>
<td>2018</td>
</tr>
<tr>
<td>Lebrikizumab</td>
<td>Anti-IL13</td>
<td>Roche</td>
<td>1,508</td>
<td>50%</td>
<td>754</td>
<td>2017</td>
</tr>
<tr>
<td>Reslizumab</td>
<td>Anti-IL5</td>
<td>Teva</td>
<td>550</td>
<td>100%</td>
<td>550</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Totals:</strong></td>
<td></td>
<td></td>
<td><strong>$9,201</strong></td>
<td></td>
<td><strong>$6,963</strong></td>
<td></td>
</tr>
</tbody>
</table>

Sales in USD based on CHF 0.96, GBP 1.55, Eur 1.11  
**Source:** BofA Merrill Lynch Global Research
Despite current treatment options ~32 million patients with uncontrolled asthma remain susceptible to exacerbations which are usually induced by viral infection.

Major Markets: US, EU, Japan, Brazil, Russia, India, China

Source: Artisan Healthcare Consulting market research study
Current asthma biologics focused on limited set of mechanisms Targeting Th2 and eosinophil (EOS) driven phenotypes

- Significant overlap exists between addressable patient populations
- Lack of validated biomarkers to guide clinical treatment to those most likely to benefit

IL-25 MOA focused on initiation of exacerbation rather than phenotype
IL-25 plays a pivotal role in initiating the immune response following viral infection of the bronchial epithelium

Expression of epithelial cytokine IL-25 following RV infection triggers initiation of (type 2) lung inflammation

There is strong biological rationale for anti-IL25 mAbs in type 2 driven disease.

Blocking IL-25 with a murine anti-IL-25 mAb prevents airway type-2 inflammation in allergic asthma model in mice (e.g., less IL-5 and IL-13 production)

Source: Ballantyne, McKenzie JACI 2007
And evidence supports investigating anti-IL-25 mAbs in the clinical management of asthma.

Bronchial epithelial expression of IL-25 but not IL-33 or TSLP is increased in asthmatics.

Source: Cheng et al AJRCCM 2014
Recent *in vivo* data suggests a pivotal role for IL-25 in rhinovirus-caused asthma exacerbations

*IL-25 expression is induced in response to RV infection and is greater in patients with asthma*

![Graph showing IL-25 expression in asthma and healthy individuals before and after infection](image)

*Beale, Bartlett et al Science Translational Medicine, 2014*
… and adds to the substantial body of research that validates IL-25 as a target in asthma

- **Hurst et al, 2002**: IL-25-adenovirus infected mice develop eosinophilia
- **Fort et al, 2001**: Repeated intraperitoneal treatment with recombinant IL-25 caused splenomegaly and gut inflammation driven by serum IgE production, eosinophilia, and upregulation of the type-2 cytokines; IL-4, IL-5, and IL-13
- **Kim et al, 2002**: Transgenic mice overexpressing human IL-25 develop eosinophilia, splenomegaly, and increased IL-4 and IL-5 production
- **Want et al, 2007**: IL-25 and IL-25 receptor have been reported to be upregulated in human asthmatic lung (Wang et al, 2007)
- **Ballantyne et al, 2007**: Neutralization of IL-25 bioactivity, during both the sensitization and challenge phase in acute OVA-induced experimental lung allergy, using an anti-IL-25 monoclonal antibody, resulted in complete suppression of airways hyper-reactivity and a significant reduction in type-2 cytokine production, lung cell infiltration, and airways mucus production.
- **Kouzaki et al, 2013**: IL-25 is stored intracellularly in airway epithelial cells, and is released upon exposure to many allergens. IL-25 transcription is also increased.
- **Yao et al, 2015**: IL-25 induces proliferation and expression of collagen I and III and smooth muscle α-actin in primary human lung fibroblasts
- **Corrigan et al, 2011**: IL-25 is elevated in asthma and contributes to angiogenesis, at least partly by increasing endothelial cell VEGF/VEGF receptor expression
- **Yao et al, 2015**: Administration of IL-25 to lungs is sufficient to cause functionally relevant airway remodeling
- **Jung et al, 2009**: IL-17RB gene polymorphism and lower receptor expression genetically associated with asthma protection
Blocking IL-25 presents a significant opportunity in uncontrolled asthma market

Only IL-25 mAb in development

Significant competition in late acting type 2 cytokine mAb market
IL-25 is a different approach: targeting the initiation of viral induced asthma exacerbation

(1) Prevent Rhinovirus (RV) Infection
- Viruses cause at least 80% of asthma exacerbations and RV by far the most common
- Vaccine, anti-viral drugs, receptor blockade
- Not currently an option due to viral diversity

(2) Target Epithelial Expressed Cytokines Directly
- BEC (bronchial epithelial cells) release IL-25 in response to viral infection
- Single target – upstream of other T\(_H\)2 cytokines
- Possibility of reducing or eliminating the effects of all downstream cytokines simultaneously
- Potential for directly treating airways

(3) Target Proximal T\(_H\)2 Cytokines (IL-4, IL-5 and IL-13)
- Current approach pursued by multiple companies
- Cannot target all cytokines simultaneously
- Mixed clinical results (disease phenotype dependent)
- Not clear if preventing viral exacerbations

Asthma Exacerbation
- Inflammation
- Mucus Production
- Bronchial reactivity

Abeome Antibody Inhibits IL25 Signalling

Virus eg rhinovirus

Bronchial Epithelial Cells (BEC)
Why is IL-25 a better target than other epithelial expressed, asthma initiating cytokines IL-33 and TSLP?

**IL-25 canonical expression and secretion pathway is well understood**
- IL-33 protein stores in the nucleus. Regulates transcription, secretion pathways unclear, potentially involves cell death/necrosis

**IL-25 receptor expressed on target type-2 cytokine producing cells**
- Stronger evidence for TLSP in Th2 polarization rather than activation of existing type-2 inflammation (exacerbation).
- IL-33 receptor expressed on many cells types highlighting a diverse role for this cytokine

**IL-25 protein structure is well defined (IL-17 family member)**
- IL-33 has multiple splice variants and cleaved extracellularly by proteases expressed by inflammatory cells; the cleaved forms are differentially active
- IL-33 oxidises rapidly and loses activity – implications for role in disease unclear
Why has development of an anti-IL-25 antibody lagged behind other antibodies involved in type-2 inflammation?

“Difficult” to make high-affinity neutralizing antibodies against IL-25

- Extremely high amino acid and structural similarity between human and mouse IL-25 makes generation of neutralizing antibodies in normal mice difficult

- Numerous post-translational modifications to IL-25 protein render some antibodies inactive against native protein

- IL-25 protein itself is hard to work with, needs to be dissolved in acid at working concentration for lab procedures

- Immunization with IL-25 protein negatively impacts immune response and creates pathology in mouse
AbeoMouse™ platform yielded multiple potent neutralizing anti-IL25 monoclonal antibodies with cross-species specificity

<table>
<thead>
<tr>
<th>Anti-IL-25 mAbs</th>
<th>Potency* IC₅₀ in HT29 Cell Assay (µg/ml)</th>
<th>Affinity* SPR</th>
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<tbody>
<tr>
<td></td>
<td>Human (E.coli)</td>
<td>Human (HEK)</td>
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<tr>
<td>ABM109.2**</td>
<td>0.042</td>
<td>20</td>
</tr>
<tr>
<td>ABM125</td>
<td>0.3</td>
<td>0.075</td>
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<tr>
<td>ABM125.9**</td>
<td>0.041</td>
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</tr>
<tr>
<td>ABM126</td>
<td>0.87</td>
<td>1.45</td>
</tr>
<tr>
<td>ABM126.4**</td>
<td>0.21</td>
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</table>

*Potency determined for human IL-25 made from both human (HEK) and bacterial (E.coli) sources; Potency and Affinity determined for mouse IL-25 made from mouse (NSO) source

**Humanized antibody
Two key pharmacology studies conducted by Abeome support the therapeutic potential of an anti-IL-25 antibody

ABEOME PRINCIPAL INVESTIGATOR | MOUSE & HUMAN BEC STUDIES

Dr. Nathan Bartlett is Head of the Viral Immunology and Respiratory Disease group based at the Hunter Medical Research Institute, Australia where he is continuing his research on the pathogenesis of rhinovirus infections and development of new treatment approaches for asthma exacerbations. He also retains an honorary academic appointment within the National Heart and Lung Institute, at Imperial College London, UK. He is an expert on pre-clinical models of respiratory virus infection in chronic respiratory diseases and was the first to define a role for IL-25 in RV-induced exacerbations of asthma.

1. Ex Vivo Validation of IL-25 Mechanism of Action in Air-Liquid Interface (ALI)-differentiated Primary Human Bronchial Epithelial Cells (BECs)
   - BECs from normal and asthmatic volunteers
   - BECs infected with minor and major group rhinovirus (RV)
   - Measure range of IL-25 expression in both groups in response to RV infection
   - Evaluate efficacy of Abeome anti-IL-25 mAbs in blocking Th2 immune response in ALI-BEC cultures

   Data Presented February 2017 (Keystone, CO)

2. In vivo Mouse Model of RV induced exacerbation of allergic airways inflammation (asthma)
   - Evaluate the efficacy anti-IL-25 mAbs (ABM125) in preventing RV induced asthma exacerbations in mouse model

   Data Presented February 2017 (Keystone, CO)
Study 1: Ex Vivo-Air-liquid interface (ALI) culture of asthmatic bronchial epithelial cells (BECs)
Study 1: *Ex Vivo*: Clinical and immunological characteristics of asthmatic pBEC donors

<table>
<thead>
<tr>
<th>Donor i.d.</th>
<th>GINA stage</th>
<th>Age</th>
<th>Sex</th>
<th>Exacerbation in last 12mths</th>
<th>OCS use</th>
<th>FEV1% predicted</th>
<th>FVC% predicted</th>
<th>Atopy</th>
<th>Sputum neuts</th>
<th>Sputum eos</th>
<th>Sputum macs</th>
<th>Age of Asthma Onset</th>
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<tbody>
<tr>
<td>AS090</td>
<td>Moderate Persistent</td>
<td>66</td>
<td>F</td>
<td>0</td>
<td>0</td>
<td>67</td>
<td>88</td>
<td>?</td>
<td>41.75</td>
<td>43.5</td>
<td>9.25</td>
<td>?</td>
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<tr>
<td>AS170</td>
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<td>2</td>
<td>79</td>
<td>87</td>
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<td>3.75</td>
<td>23.75</td>
<td>Childhood</td>
</tr>
<tr>
<td>AS131</td>
<td>Mild Persistent</td>
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<td>F</td>
<td>1</td>
<td>1</td>
<td>89</td>
<td>89</td>
<td>Yes</td>
<td>5</td>
<td>3.75</td>
<td>89.25</td>
<td>?</td>
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<tr>
<td>AS140</td>
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<td>F</td>
<td>3</td>
<td>0</td>
<td>101</td>
<td>98</td>
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<td>77</td>
<td>3</td>
<td>20</td>
<td>Childhood</td>
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<tr>
<td>AS153</td>
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<td>F</td>
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<td>0</td>
<td>85</td>
<td>97</td>
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<td>5</td>
<td>44.5</td>
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<tr>
<td>AS178</td>
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<td>M</td>
<td>0</td>
<td>0</td>
<td>74</td>
<td>75</td>
<td>No</td>
<td>11.75</td>
<td>5</td>
<td>27.25</td>
<td>Childhood</td>
</tr>
</tbody>
</table>
Study 1: Ex Vivo: IL-25 expression is higher at baseline and is induced by rhinovirus in asthma patients but not in healthy volunteers

- Asthmatic ALI-differentiated epithelial cultures were infected with major group RV43 or minor group RV1B
- IL-25 mRNA levels over four days were assessed by qPCR.
Study 1: *Ex Vivo*: Highest IL-25 expression in cells from severe (Sev) and moderate (Mod) asthmatics

Data is expressed as mean +/- SEM

**p<0.01** for RV43 infected cells compared to mock infected cells at day 4 p.i. (non-parametric t test)
Study 1: *Ex Vivo*: Type-2 inflammatory mediators (CCL5 and CCL22) track with IL-25 expression - not with IL-33 expression
Study 2: Mouse Model of rhinovirus-induced exacerbation of allergic airways inflammation with anti-IL-25 (ABM125) treatment before infection

Mice were sensitized with low LPS hen egg ovalbumin (OVA 50μg in 2mg alum) and then challenged with 50μg OVA intranasally (i.n.) on three consecutive days. Directly after the final OVA challenge mice were administered ABM125 or isotype control (IgG) intraperitoneally (i.p.). Four hours after mAb dosing mice were infected i.n. with $2.5 \times 10^6$ TCID$_{50}$ RV1B. Inflammatory responses were assessed at day three post infection.
Study 2: Single Dose - Significant decrease in lung inflammation in ABM125 treatment group (500µg)

Total BAL After Infection and Therapeutic Antibody Treatment

- OVA+PBS+Mock
- OVA+PBS+RV
- OVA+ABM125+Mock
- OVA+ABM125+RV

Total BAL cells (x10^5/mL)

BAL Eosinophils After Infection and Therapeutic Antibody Treatment

- OVA+PBS+Mock
- OVA+PBS+RV
- OVA+ABM125+Mock
- OVA+ABM125+RV

Total lung infiltrating cells

Eosinophils
Study 2: Dose-Response - ABM125 treatment before rhinovirus infection significantly reduces lung inflammation in a dose-dependent manner.
Study 2: Dose Response – Trend for decrease in IL-5 expression in response to ABM125 treatment
Study 2: ABM125 treatment reduces rhinovirus levels in lung

*Promoting clearance of virus represents a possible competitive advantage for ABM125*

\[\text{Rhinovirus RNA (copies/mL cDNA)}\]

\[p = 0.02\]
Summary & Conclusions from Study 1 and Study 2

- ALI-differentiated asthmatic epithelium responds to RV infection with elevated IL-25, which was associated with more severe disease.

- Epithelial IL-25 was also associated with increased levels of the related type-2 inflammatory mediators, CCL5 and CCL22.

- Neutralizing IL-25 *in vivo* with mAb ABM125, suppressed airway eosinophil recruitment in a model of RV-induced exacerbation of allergic airways disease.

- Reduced eosinophilic inflammation was associated with a trend towards reduced IL-5 mRNA expression.

- RV-infected mice treated with ABM125 had less viral RNA in their lungs.
Two IL-5 antibodies have been approved in severe asthma and are indicated for use in patients with elevated blood eosinophils (EOS)

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Company</th>
<th>Target</th>
<th>Approved Patient Population</th>
<th>Dose</th>
<th>Primary Endpoints in Pivotal Trials</th>
<th>Patients¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucala</td>
<td>GSK</td>
<td>IL-5</td>
<td>• Severe Asthma&lt;br&gt;• &gt;12 years old&lt;br&gt;• Elevated EOS</td>
<td>100mg SubQ Every 4 wks</td>
<td>• Exacerbation Frequency&lt;br&gt;• Steroid Use&lt;br&gt;• Hospital Stays/Visits</td>
<td>1,357</td>
</tr>
<tr>
<td>Cinqair</td>
<td>Teva</td>
<td>IL-5</td>
<td>• Severe Asthma&lt;br&gt;• &gt;18 years old&lt;br&gt;• Elevated EOS</td>
<td>3mg/kg IV Every 4 wks</td>
<td>• Exacerbation Frequency&lt;br&gt;• Lung Function (FEV1)</td>
<td>981</td>
</tr>
</tbody>
</table>

¹Patients evaluated for approval in BLA submission
Clinical path to commercial success for ABM125 based on IL-25 novel mechanism of action

Phase 1

• Safety, pharmacodynamics and pharmacokinetic (ADME) data to support subcutaneous administration

Phase 1/2

• Efficacy of IL-25 antibody administration prior to experimental rhinovirus infection in asthmatic volunteers with history of exacerbations in preventing or reducing severity of exacerbations (Therapeutic Frontiers in UK)
  • Placebo vs ABM125 (15-20/arm)
  • Endpoints: Lower respiratory symptom score (LRSS), lung function, immune response

Phase 2B/3

• Idiopathic Pulmonary Fibrosis
• Atopic dermatitis

Phase 3

• Based on results of rhinovirus challenge study conduct comparative studies in poorly controlled asthmatics susceptible to exacerbations
  • Treatment with ABM125 mAb following naturally acquired rhinovirus infection
  • Prophylactic treatment with ABM125 mAb

1 Orphan Drug Indication
Why Abeome?

- Our anti-IL-25 mAb (ABM125) has the potential to provide a new treatment approach for uncontrolled asthma
  - Global asthma market projected to be $22B by 2024, with up to $9B of new sales driven by biologics
  - Abeome’s anti-IL-25 antibody has the potential to prevent or treat asthma exacerbations which are usually caused by the common cold virus providing a potential competitive advantage and differentiation from other, later-acting type 2 cytokine mAbs (IL-4, IL-5, and IL-13)

- Product-focused early stage company with therapeutic mAbs for both validated and novel targets
  - Partnership opportunities exist on programs covering targets in Immune Disease (IL-17A), Immuno-oncology (PD-L1, OX-40, novel T-Cell Agonists), and Hypercholesterolemia (novel anti-PCSK9 mAbs)
  - Early research on obesity (antibody to pre-adipocytes) has also generated partnership interest

- Proprietary platform to rapidly discover functional high-affinity antibodies allows Abeome the ability to diversify its pipeline
  - Using AbeoMouse™, we can progress from immunization to functional, high-affinity antibodies in ~3 months
  - Makes Abeome an ideal partner for discovery collaborations

- Experienced Team
  - Product-focused team with experience at Amgen, Genentech, CuraGen, Kythera Biopharmaceuticals, and Dendreon
  - This team has brought products to market, taken companies public, collectively raised over $750M, and completed multiple large pharma deals.