Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)
Inhaled therapeutic leadership; spearheading immunology biologics

Bing Yao, Head of MedImmune Respiratory, Inflammation & Autoimmunity iMED
Respiratory: Transform patient outcomes in asthma, COPD & IPF

1. Deliver inhaled therapies
   - Short term

2. Expand with innovative precision therapies
   - Medium term

3. Transforming disease management
   - Long term
### Respiratory: Industry-leading portfolio

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III / Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small molecule</td>
<td>Large molecule</td>
<td>Small molecule</td>
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<tr>
<td>AZD1419 TLR9</td>
<td>brodalumab* IL17R</td>
<td>benralizumab IL5R severe asthma</td>
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<td>COPD</td>
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<tr>
<td>AZD7624 ip38</td>
<td>AZD9412 Inhaled IFNβ</td>
<td>PT003 LAMA/LABA COPD</td>
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<tr>
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<td>COPD</td>
</tr>
<tr>
<td>AZD7594 iSGRM</td>
<td>MEDI9929* TSLP</td>
<td>benralizumab IL5R</td>
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<tr>
<td>PT010 LAMA/LABA/ICS</td>
<td>AZD9412 Inhaled IFNβ</td>
<td>Duaklir LAMA/LABA COPD</td>
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<tr>
<td>AZD8999 MABA</td>
<td>PT010 LAMA/LABA/ICS</td>
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<tr>
<td></td>
<td>asthma</td>
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<tr>
<td>AZD8999 MABA</td>
<td>PT008 ICS</td>
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<tr>
<td></td>
<td>COPD</td>
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<tr>
<td>AZD8999 MABA</td>
<td>AZD0548 (abecloterol) LABA</td>
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<td>COPD</td>
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<tr>
<td></td>
<td>PT009 ICS/LABA</td>
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<tr>
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</tbody>
</table>

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3 – Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)
COPD: Inhaled portfolio addresses all disease severities and provides device choice

Diagnosed with exacerbation

Diagnosed with symptoms

Symptoms worsening

Increased risk of exacerbation

Adapted from GOLD guidelines

"Passive" dry powder inhaler, DPI, most commonly used

"Active" device, pMDI, preferred for elderly and for severe disease

4 – Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)
Asthma: Inhaled portfolio addresses all GINA steps and provides device choice

![Diagram showing GINA classification and device choices]

- **LAMA/ICS**
- **LAMA/LABA/ICS**

GINA classification:
1. "Passive" dry powder inhaler, DPI, most commonly used
2. 'As Needed'
3. LABA/ICS
4. ICS
5. "Active" device, pMDI, preferred for young, elderly and for severe disease

Adapted from GINA guidelines
Severe asthma: Targeting distinct patient subsets

Blood eosinophil level

Serum periostin level

High

Low

Th2 driven | EOS low

B 20%

Anti-IL-13

Th2 driven | EOS dominant

A 35%

Anti-IL-5

Anti-IL-13

Th2 low | EOS low

D 30%

Anti-IL-13

Th2 low | EOS high

C 15%

Anti-IL-5

30% 20% 35%
Benralizumab (severe asthma): Only IL5 receptor mAb in Phase III

Phase IIb data

- Potent reduction in eosinophils
- Reduction in asthma exacerbation
- Improvement in lung function

Exacerbation rate reduction

Annual exacerbation rate reduction relative to placebo

Baseline blood eosinophil count cutoff (cells per μL)

Regulatory submission expected 2016

Source: M. Castro et al., Lancet Resp Med, 2014
Benralizumab (COPD): First mAb to show eosinophilic inflammation reduction

Phase Ila data

- First anti-IL5 / IL5R to demonstrate lung function improvement
- Primary endpoint not achieved, but trend toward reduction of exacerbations with elevated eosinophils
- Improvement in symptom scores

Mean change from baseline in FEV1 over time (PP population)

Phase III on track for completion 2018

Source: Brightling et al., Lancet Resp Med, 2014
Tralokinumab (severe asthma): Targeting IL13, a central TH2 cytokine

- Identified potential responder population
- Identified promising biomarkers
- Efficacy across AER, FEV1, ACQ-6 and AQLQ in subgroups

AER for tralokinumab 300 mg Q2W vs placebo over 52 weeks

- Periostin-low (15):
  - 32%
  - (273, -53)
- DPP-4 low (8):
  - 7%
  - (886, -88)

- All (33):
  - -44%
  - (-22, -74)
- Periostin-high (18):
  - -67%
  - (-2, -89)
- DPP-4 high (24):
  - -57%
  - (273, -53)

Phase III on track for completion 2017
Phase II ongoing in IPF

AER – Asthma Exacerbation Rate, FEV1 – Forced Expiratory Volume in 1 second, ACQ-6 – Asthma Control Questionnaire, AQLQ – Asthma Quality of cycle Questionnaire
Inflammation & Autoimmunity: 
Series of first & best-in-class assets

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<tr>
<td><strong>Large molecule</strong></td>
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<td><strong>Large molecule</strong></td>
</tr>
<tr>
<td>MEDI5872* B7RP1 SLE</td>
<td>mavrilimumab GM-CSFR rheumat arthritis</td>
<td>brodalumab* IL17R psoriasis arthritis</td>
</tr>
<tr>
<td>MEDI4920 CD40L Sjögren's</td>
<td>sifalimumab IFNa SLE</td>
<td>lesinurad SURI gout</td>
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<tr>
<td>MEDI-551 CD19 MS</td>
<td>anifrolumab IFNaR SLE</td>
<td>brodalumab* IL17R psoriasis</td>
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</table>

**Small molecule**

<table>
<thead>
<tr>
<th>Phase II</th>
<th>Phase III / Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RDEA3170 SURI gout</td>
</tr>
</tbody>
</table>

**Disease area**

- Rheumatology
- Dermatology
- Gastroenterology
- Neuroscience

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10 – Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)
Lesinurad (gout): Progressing to regulatory submission

Lesinurad in gout

- Gout affects ~15m patients
  - Potential to cause bone, joint, kidney damage and associated with CV disease and its co-morbidities
- Xanthine oxidase (XO) inhibitors act to control production of uric acid
- 40–70% of patients are not at goal on XO inhibitors alone
- Lesinurad and RDEA3170 increase excretion of uric acid
- RDEA3170 Ph II studies progressing with focus in mono and FDC
- Lesinurad EU / US submission planned Q4 2014 for use w/XO

CLEAR 1 and CLEAR 2: Proportion of patients achieving sUA <6 mg/dL at Month 6 – NRI

- AE profile, incl. renal AE of lesinurad 200mg+allopurinol comparable to allopurinol alone
- Increases in serum creatinine observed lesinurad 200mg plus allopurinol vs. allopurinol alone (5.9-6.0% vs. 1.0-3.4%, >1.5x increase vs. baseline)
Targeting IFNα / IFNαR in lupus

Sifalimumab binds directly to IFNα neutralising IFNα subtypes

Anifrolumab targeting broader spectrum of interferons (IFNα, IFNβ, and IFNω)

Phase IIb lupus study validates interferon targeting: Primary and secondary endpoints achieved

Receptor-targeting potentially better efficacy: Greater PD suppression (70–90% vs. 30–40% for sifalimumab)

Anifrolumab Phase II presentation expected mid-2015
Phase III start expected 2015
Sifalimumab (lupus): Significant improvement in SLE responder index and organ specific measurements

<table>
<thead>
<tr>
<th>Endpoint at day 365</th>
<th>SRI (4)</th>
<th>SRI (6)</th>
<th>SRI (8)</th>
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<tbody>
<tr>
<td><strong>All-comers population</strong></td>
<td></td>
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</tr>
<tr>
<td>Placebo (%) (N=98 - 108)</td>
<td>45.4</td>
<td>37.4</td>
<td>24.5</td>
</tr>
<tr>
<td>1200 mg dose (%) (N=98 - 107)</td>
<td>59.8</td>
<td>53.3</td>
<td>41.8</td>
</tr>
<tr>
<td>Effect size (%)</td>
<td>14.4</td>
<td>15.9</td>
<td>17.3</td>
</tr>
<tr>
<td>P-value*</td>
<td>0.031</td>
<td>0.016</td>
<td>0.008</td>
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<tr>
<td><strong>Dx+ population</strong></td>
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<td></td>
</tr>
<tr>
<td>Placebo (%) (N=79 - 88)</td>
<td>42.0</td>
<td>33.3</td>
<td>20.3</td>
</tr>
<tr>
<td>1200 mg dose (%) (N=80 - 87)</td>
<td>57.5</td>
<td>51.7</td>
<td>41.3</td>
</tr>
<tr>
<td>Effect size (%)</td>
<td>15.4</td>
<td>18.4</td>
<td>21.0</td>
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<tr>
<td>P-value*</td>
<td>0.038</td>
<td>0.012</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*SRI(x) SLE Responder Index(x= reduction in SLEDAI required for response)*

**P-value < 0.098 is considered to be statistically significant for the final analysis after adjusting for the interim analysis using O’Brien-Fleming type Lan-DeMets alpha spending function approach to control type I error rate at 0.1 for the primary endpoint**

**mITT Population with a CLASI Activity Score ≥10 at Baseline**

Day 1

Day 169

24.5% treatment difference in CLASI-4 response 1200 mg dose vs placebo**
Mavrilimumab (RA): First-in-class anti-GM-CSFRα antibody

Phase IIb data

- 45–74% of patients on anti-TNF fail to achieve an ACR50
- Mavrilimumab inhibits macrophage activation, differentiation and survival

Phase IIb results

- Co-primary endpoints: DAS28, ACR20 highly significant
- Significant benefit after one week
- Significant improvements in patient-reported outcomes
- No apparent safety signals


ACR efficacy responses at day 169

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=81)</th>
<th>Mav. 30mg (N=81)</th>
<th>Mav. 100mg (N=85)</th>
<th>Mav. 150mg (N=79)</th>
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</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>24.7</td>
<td>50.6</td>
<td>61.2</td>
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<tr>
<td>ACR50</td>
<td>12.3</td>
<td>28.4</td>
<td>25.9</td>
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<tr>
<td>ACR70</td>
<td>3.7</td>
<td>12.3</td>
<td>10.6</td>
<td>13.9</td>
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</table>

ACR 2014 oral presentation
Brodalumab (psoriasis, psoriatic arthritis, asthma): Unique receptor-targeting approach

**Psoriasis**
- Three Phase III studies; two with H2H superiority study design vs. Stelara (ustekinumab) and placebo
- First and second Phase III studies achieved primary and secondary endpoints
- Remaining Phase III psoriasis H2H comparator data in Q4 2014

**Psoriatic arthritis**
- Phase III on track

**Asthma**
- Opportunity for lifecycle management

Targeting IL17 receptor and inhibiting signaling of multiple ligands

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Brodalumab (psoriasis):
Positive Phase III data

AMAGINE-1™ Phase III psoriasis data may offer new level of skin clearance

### AMAGINE-1™ Phase III psoriasis data

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PASI 100</th>
<th>PASI 90</th>
<th>PASI 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (N=81)</td>
<td>23.3</td>
<td>41.9</td>
<td>70.3</td>
</tr>
<tr>
<td>Broda. 140mg</td>
<td>42.5</td>
<td>70.3</td>
<td>83.3</td>
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<tr>
<td>Broda. 210mg</td>
<td>0.5</td>
<td>0.9</td>
<td>2.7</td>
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</table>

### AMAGINE-3™ Phase III H2H ustekinumab comparator

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PASI 100</th>
<th>PASI 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.3</td>
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<tr>
<td>Ustekinumab</td>
<td>18.5</td>
<td>27.0</td>
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<tr>
<td>Broda. 140mg</td>
<td>36.7</td>
<td></td>
</tr>
<tr>
<td>Broda. 210mg</td>
<td>69.2</td>
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</tbody>
</table>

Phase III AMAGINE-2™ H2H comparator study expected in Q4 2014

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Respiratory, Inflammation & Autoimmunity: Lifecycle management of first & best-in-class medicines

Highlighted Phase III and Phase II molecules:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication(s)</th>
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<tbody>
<tr>
<td>benralizumab</td>
<td>severe asthma, COPD</td>
</tr>
<tr>
<td>tralokinumab</td>
<td>severe asthma, IPF</td>
</tr>
<tr>
<td>brodalumab*</td>
<td>psoriasis, psoriatic arthritis, asthma</td>
</tr>
<tr>
<td>sifalimumab/anifrolumab</td>
<td>SLE, lupus nephritis, myositis, Sjögren’s</td>
</tr>
<tr>
<td>MEDI7183*</td>
<td>Crohn’s disease, ulcerative colitis</td>
</tr>
</tbody>
</table>

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Lead indication | LCM pursuing now | LCM for future

17 – Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)
### 2015: Duaklir launch, potential approval, submissions and Phase III starts

| **Duaklir** | Launch of LAMA-LABA in Genuair device in EU |
| **Ilesinurad** | Potential approval of first new MOA for gout in combination with XO |
| **Brodalumab*** | Submission of IL17R for psoriasis |
| **PT003** | Submission of first pMDI LAMA-LABA |
| **Phase III starts** | PT010 triple COPD, sifalimumab/anifrolumab, mavrilimumab |

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Summary

Strong respiratory portfolio broadened through Pearl and Almirall

Positive data for first and best-in-class molecules in portfolio

Most comprehensive portfolio of personalised precision therapies
Pipeline: Respiratory, Inflammation & Autoimmunity (RIA)

Inhaled therapeutic leadership; spearheading immunology biologics

Bing Yao, Head of MedImmune Respiratory, Inflammation & Autoimmunity iMED