Safety, PK and PD of ARRY-502, a CRTh2 Antagonist, in Healthy Subjects with a History of Seasonal Allergies

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PGD$_2$ is a potent prostanoid released upon mast cell activation
  - Links early & late phase allergen responses

CRTh2 is the biologically relevant GPCR for PGD$_2$ & its more stable metabolites
  - Chemoattractant Receptor-homologous molecule expressed on Th2 lymphocytes
CRTh2 Antagonism: Target Validation

- **CRTh2 knockout mice**
  - Diminished responses to allergic challenge with decreased IL-4, IL-13, IgE, mucus production, eosinophil migration, airway hyperresponsiveness

- **Selective CRTh2 antagonists have demonstrated preclinical efficacy**
  - Significant reduction of eosinophil accumulation in OVA-sensitized mice model of asthma
  - Reduction in cell infiltrates and cytokines in skin in a cutaneous OVA & FITC mouse models of dermatitis
  - Reduction in pulmonary neutrophilia in a cigarette-smoke mouse model of COPD

- **Ramatroban®, a weak, non-selective CRTh2 antagonist, is approved for allergic rhinitis (Japan)**
  - Improved the symptoms, nasal obstruction & daily discomfort compared to terfenadine in a Phase 3 study

- **OC000459, a selective CRTh2 antagonist, improved lung function in mild to moderate asthmatics in a Phase 2a study**
  - FEV1 increased over baseline by 9.2% (treatment) vs. 1.8% (placebo)
  - FEV1 did not plateau – still improving at week 4
  - Significant improvement in peak expiratory flow
  - Significant decreases in serum IgE & sputum eosinophil counts
  - No serious AE’s
**ARRY-502: *In Vitro* Potency, Selectivity and Functional Activity**

<table>
<thead>
<tr>
<th>Test Description</th>
<th>IC$_{50}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human CRTh2 Binding IC$_{50}$</td>
<td>1 nM</td>
</tr>
<tr>
<td>Human CRTh2 Binding IC$_{50}$ (4% HSA)</td>
<td>35 nM</td>
</tr>
<tr>
<td>Selectivity vs. 30 GPCR’s, Ion Channels and Transporters</td>
<td>No significant activity @500 nM</td>
</tr>
<tr>
<td>CRTh2 FLIPR Calcium Mobilization IC$_{50}$</td>
<td>5 nM</td>
</tr>
<tr>
<td>Human Isolated Basophil Chemotaxis IC$_{50}$</td>
<td>1 nM</td>
</tr>
<tr>
<td>Murine Models of Allergic Rhinitis, Asthma &amp; Atopic Dermatitis</td>
<td>ED$_{50}$’s &lt; 30 mg/kg</td>
</tr>
<tr>
<td>Human Whole Blood Receptor Internalization IC$_{50}$</td>
<td>22 nM</td>
</tr>
<tr>
<td>Human Whole Blood Eosinophil Shape Change IC$_{50}$</td>
<td>58 nM</td>
</tr>
</tbody>
</table>
ARRY-502 Single-Ascending Dose (SAD) Study Design

- Randomized, double-blind (Sponsor-exempt), placebo-controlled, single ascending dose study in healthy subjects with a history of seasonal allergies
  - Adult males and females, 18-50 years old
    - Total number of subjects = 24
    - 3 Cohorts
      - 6 subjects received ARRY-502 and 2 received placebo
  - Mid-dose cohort crossover food effect assessment
    - fasted versus FDA high-fat meal
  - 100, 200 and 400 mg single doses
  - Safety assessments included clinical observations, laboratory assessments, ECGs and adverse events
Pharmacodynamic Assessments

- To monitor pharmacodynamic activity of ARRY-502, blood samples were collected at Day -1, Day 1 predose, 1, 2, 8 and 24 hours

- Blood was stimulated ex vivo +/- PGD$_2$ and processed for eosinophil shape change (ESC) and CRTh2 receptor internalization (RI)

PGD$_2$ exposed to eosinophils in whole blood results in a shape change
- Activation of the intracellular motile apparatus
- Occurs exclusively through CRTh2
ARRY-502 SAD Safety Summary

- All AEs were mild, short in duration and transient
- No significant laboratory or cardiovascular changes
- ARRY-502 was well tolerated at all doses evaluated

<table>
<thead>
<tr>
<th>Adverse Event (MedDRA PT)</th>
<th>100 mg N=6</th>
<th>200 mg (fasted) N=6</th>
<th>200 mg (fed) N=5</th>
<th>400 mg N=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal dreams</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asthenia</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dizziness</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
**ARRY-502 SAD Pharmacokinetic Summary**

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1</th>
<th>Cohort 2 Period 1</th>
<th>Cohort 2 Period 2</th>
<th>Cohort 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>1,920 (47)</td>
<td>3,760 (41)</td>
<td>3,300 (39)</td>
<td>7,280 (42)</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (hr)</td>
<td>4 (3-4)</td>
<td>4 (3-6)</td>
<td>4 (4-8)</td>
<td>4 (2-6)</td>
</tr>
<tr>
<td>( \text{AUC}_{\text{all}} ) (hr*ng/mL)</td>
<td>11,700 (31)</td>
<td>20,580 (38)</td>
<td>18,800 (25)</td>
<td>31,910 (47)</td>
</tr>
<tr>
<td>( t_{1/2} ) (hr)</td>
<td>17 (12-27)</td>
<td>23 (18-45)</td>
<td>19 (16-31)</td>
<td>12 (8-43)</td>
</tr>
</tbody>
</table>

\( C_{\text{max}} \) and AUC are the Geometric Mean (%CV)
\( T_{\text{max}} \) and \( t_{1/2} \) are the Median (Min, Max)
There was increasing exposure with increasing dose, which was approximately dose proportional based upon $C_{\text{max}}$ and slightly less than based upon $\text{AUC}$.

$T_{\text{max}}$ was consistent across the doses evaluated.

Low inter-subject variability was observed.

The metabolite to parent ratio was low (~1%) and consistent across the doses evaluated (data not shown).

There was not a statistically significant food effect observed between the fasted (Period 1) and fed (Period 2) subjects.
Pharmacodynamic assessment indicates inhibition of eosinophil shape change and CRTh2 receptor internalization at all doses evaluated.

The lack of dose response observed indicates that the maximal effect (complete inhibition) has been achieved following a single dose.

All subjects receiving ARRY-502 responded in PD assays, even those with low receptor expression.
The determined IC$_{50}$ values for ESC and RI are in good agreement with previous in vitro values.

Eosinophil Shape Change
IC$_{50}$ = 128 ng/mL (248 nM)

Receptor Internalization
IC$_{50}$ = 19 ng/mL (37 nM)
Also, based upon the terminal half-life of ARRY-502 and modeling, an increase in AUC upon repeat dosing is predicted.

- At steady state, 400 mg QD, 24 hour trough may be ~ 240 nM
Summary

- CRTh2 is a key GPCR for PGD$_2$ and is emerging as an effective drug target to treat allergic disease

- ARRY-502 is a potent, selective CRTh2 antagonist

- ARRY-502 has good oral exposure in normal healthy volunteers

- ARRY-502 is well tolerated at doses of 100, 200 and 400 mgs

- ARRY-502 demonstrates good pharmacodynamic activity upon QD dosing
  - 24-Hour target coverage and prolonged pharmacodynamic activity is expected upon multiple QD dosing