Th2 Signature Selection Strategies for CRTh2 Antagonists: Baseline Characteristics of a Mild to Moderate Persistent Asthma Population

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Rationale:

**CRTh2 (DP2)** is a G protein-coupled receptor that is expressed on many cell types associated with the pathophysiology of allergic asthma including Th2 T cells, basophils, and eosinophils. Several small molecule antagonists of CRTh2 are currently in clinical development for the treatment of asthma but to date have shown only modest clinical activity. It is now recognized that the traditional view of “allergic inflammation” represents only a subset of the asthma population, specifically those characterized by the local expression of a "Th2 signature" in their bronchial epithelium. It is therefore unlikely that targeting the CRTh2 pathway would provide robust clinical benefit in an unselected patient population. A number of approaches has been used to identify systemic biomarkers of this signature to enrich for patients who are responsive to Th2-targeted therapies such as antibodies to interleukin (IL)-5 and IL-13. These markers include fraction extracted nitric oxide (FeNO) and serum concentrations of the protein peridinin, a metabolite of PGD2. The usefulness of combined measurements of squamous cell carcinoma antigens 1 and 2 in asthma subjects compared to controls was evaluated.

**Methods:**

- Phase 2 POC study with ARRY-502, a potent and selective CRTh2 antagonist
  - 182 Mild-to-moderate asthma patients
- Trial is fully enrolled and ongoing
- Patients were enriched for atopic markers
- Phadiatop® positive
- Elevated FeNO
- Analysis of biomarkers at enrollment (before treatment) on 40 interim subjects:
  - Serum concentrations of peroxidin, squamous cell carcinoma antigen 1 (SCCA1), SCCA2 and TARC were determined by ELISA
  - Multi-parameter flow cytometry assay in whole blood allowed simultaneous determination of CRTh2 expression by CD4+ T cells, basophils and eosinophils
- 11.15-dioxy-balta-hydroxy-2,3,4,5-tetranorprostan-1,2,3-dioic acid (tPGDM; PGD2 metabolite) levels in urine determined by LC-MS
- Periostin is a metabolite of PGD2
- Represents an indirect measure of CRTh2 pathway activation
- Levels were normalized to creatinine concentrations

**Figure 1:** Regulation of Allergic Inflammation by PGD2/CRTh2

**Figure 2:** Multi-parameter Analysis of T cells, Basophilis and Eosinophils by Flow Cytometry

**Figure 3:** FeNO Levels and IgE Levels are Elevated in Mild to Moderate Persistent Asthma

**Figure 4:** Urinary tPGDM Levels in Patients versus Controls

**Table 1. Serum Markers of Th2-Associated Inflammation**

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Source</th>
<th>Median Concentration (range)</th>
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<tbody>
<tr>
<td>Periostin</td>
<td>Serum</td>
<td>46 ng/mL (23-94)</td>
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<tr>
<td>SCCA1</td>
<td>Serum</td>
<td>0.91 ng/mL (0.3-1.8)</td>
</tr>
<tr>
<td>SCCA2</td>
<td>Serum</td>
<td>0.8 ng/mL (0.2-2)</td>
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<tr>
<td>TARC</td>
<td>Serum</td>
<td>410 pg/mL (16-1689)</td>
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**TARC, SCCA1 and SCCA2 have been shown to be elevated in the serum of subjects with allergic diseases such as atopic dermatitis**

- TARC, thymus and activation regulated chemokine (a.k.a. CCL17)
- Squamous cell carcinoma antigens (SCCA) are induced by IL-4 and IL-13

**Periostin levels (>25 ng/mL) have been shown to provide a Th2 signature in severe, steroid-refractory asthma**

<table>
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<tr>
<th><strong>Summary</strong></th>
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<tr>
<td>Serum markers of allergic inflammation can be readily detected in subjects with mild to moderate persistent asthma</td>
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<td>CRTh2-positive eosinophil levels were elevated in asthma subjects when compared to controls</td>
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<td>Urinary IPGDM, a metabolite of PGD2, and a marker of CRTh2-dependent signaling, was elevated in subjects when compared to controls</td>
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<td>Serum IgE and FeNO were elevated when compared to historically reported values</td>
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<td>The ongoing ARRY-502 proof-of-concept study will provide information about whether these biomarkers will help to predict patient populations that are responsive to CRTh2 antagonists</td>
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**The levels of urinary IPGDM were significantly increased in subjects compared to controls (p<0.01)**

**These findings provide evidence for eosinophilic Th2-driven allergic inflammation and activation of the CRTh2/PGD2 pathway in selected mild-to-moderate asthma patients**