**Results (continued)**

**ARYR-502 SAD Pharmacokinetic Summary**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>AUC 0-24 (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>1,920 (47)</td>
<td>4.64</td>
<td>3,760 (41)</td>
</tr>
<tr>
<td>200 Fasted</td>
<td>3,760 (41)</td>
<td>4.64</td>
<td>7,280 (42)</td>
</tr>
<tr>
<td>400</td>
<td>7,280 (42)</td>
<td>4.64</td>
<td>14,560 (42)</td>
</tr>
</tbody>
</table>

**ARYR-502 SAD Pharmacodynamic Summary**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Human CRTh2 FLIPR Calcium Mobilization IC50</th>
<th>Human CRTh2 Binding IC50</th>
<th>Human White Blood Eosinophil Shape Change IC50</th>
<th>Human White Blood Eosinophil Receptor Internalization IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>7,280 (42)</td>
<td>1 nM</td>
<td>58 nM</td>
<td>22 nM</td>
</tr>
<tr>
<td>200 Fasted</td>
<td>7,280 (42)</td>
<td>1 nM</td>
<td>58 nM</td>
<td>22 nM</td>
</tr>
<tr>
<td>400</td>
<td>7,280 (42)</td>
<td>1 nM</td>
<td>58 nM</td>
<td>22 nM</td>
</tr>
</tbody>
</table>

**RESULTS**

**ARYR-502 SAD Safety Summary**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>100 mg</th>
<th>200 mg (Fasted)</th>
<th>200 mg (Fed)</th>
<th>400 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal dreams</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

**ABSTRACT**

Background: Prostaglandin D2 (PGD2) is derived from mast cells in response to allergens. Subsequent interaction with chemokine receptor-homologous molecule expressed on Th2 cells (CRTh2), a receptor for PGD2, mediates a number of effects of PGD2, including cell recruitment and cytokine production. Selective antagonism of CRTh2 offers a therapeutic approach for the treatment of allergic disease. ARRY-502 is a selective and potent antagonist of the CRTh2 receptor shown to be efficacious in nonclinical studies of allergic inflammation.

Methods and Objectives: This Phase 1 SAD study was designed to evaluate the primary objectives of safety and PK, along with the secondary objectives of assessing PD of ARRY-502 based upon a PGD2-stimulated ex vivo eosinophil shape change (ESC) assay and a novel receptor internalization (RI) assay. In addition, food effect on the exposure of ARRY-502 was assessed.

Results: ARRY-502 was well tolerated at all doses evaluated. PK analysis showed excellent exposure with low inter-subject variability. Plasma concentrations from the lowest planned dose were the human in vitro CRTh2 ESC assay EC50 for greater than 48 hours. PD analysis indicated exposure-related inhibition of ESC and RI, with complete inhibition in the RI assay with a sustained effect for at least 24 hours after dosing.

Conclusions: ARRY-502 was well tolerated at all doses evaluated in healthy subjects with a history of seasonal allergies. The potential efficacy of ARRY-502 was shown in the positive outcome of two PD assays. The good safety profile, along with favorable PK, make ARRY-502 a promising CRTh2 antagonist for the treatment of allergic disease.

**INTRODUCTION**

**METHODS**

**ARYR-502 Single-Ascending Dose (SAD) Study Design**

- Randomized, double-blind, placebo-controlled, single ascending dose study in healthy subjects with a history of seasonal allergies.
- Objectives were to evaluate the safety, PK and PD of ARRY-502 following a single oral dose administration in healthy adult subjects with a history of seasonal allergies.
- The primary end point was the expression of CRTh2 in peripheral blood lymphocytes and the secondary end point was the expression of CRTh2 in peripheral blood mononuclear cells.
- There was not a statistically significant food effect observed between the fasted and fed states.

**Pharmacodynamic Analysis**

- Blood was collected at various times for the purpose of characterizing the pharmacodynamics of ARRY-502 and a metabolite.
- Plasma concentration-time data for ARRY-502 were modeled using a one-compartment pharmacokinetic (PK) model with sequential PK model.
- PK parameters were based on noncompartmental analysis and WinNonLin®.
- Plasma concentration-time data for ARRY-502 were modeled using a population-based oral 2-compartment PK model (Phoenix) with lag time. Using the optimized base PK model, receptor internalization and eosinophil shape change data were modeled using an exponential model.
- There was increasing exposure with increasing dose, which was approximately dose proportional based upon Cmax and slightly less than based upon AUC.
- There was consistent across the doses evaluated.
- CRTh2 receptor expression in peripheral blood mononuclear cells was not affected by the food effect observed.
- All subjects receiving ARRY-502 responded in PD assays, even those with low receptor expression.

**ARYR-502 SAD PK/PD Relationships**

Predicted Daily ARRY-502 Concentration-Time Profiles and RI Response at Steady-State (QD Dosing)

**REFERENCES**