**Background Information**

- A highly purified population of cardiomyocytes, differentiated from human induced pluripotent stem (iPS) cells (Cellular Dynamics iCell® Cardiomyocytes), are used.

- The cells are a mixture of spontaneously electrically-active atrial, nodal and ventricular-like myocytes. They possess typical human heart cell characteristics forming electrically connected syncytial layers that beat in synchrony, and exhibit expected electrophysiological and biochemical responses upon reference drug exposure.

- Viability is maintained for an extended culture periods (up to 2 weeks) allowing for acute and chronic studies.

- Microelectrode array (MEA) is one of the most sophisticated and efficacious technologies for measuring changes in spontaneously-active cells, such as cardiomyocytes and neurons.

- Cyprotex’s eCiphr®Cardio uses microelectrode array recording to monitor electrophysiological activity by measuring beat rate, field duration potential, amplitude and conduction velocity.

- Unlike the patch-clamp hERG assay, eCiphr®Cardio assesses changes in all major ion channels implicated in an action potential.

- This cardiac assay provides a unique in vitro system for preclinical drug discovery, cardiotoxicity assessment, disease modelling and high throughput phenotypic screening of drug candidates.

**Protocol**

**Instrument**
Maestro 48-well MEA System (Axion BioSystems)

**Cell Type**
Human iPS cell-derived iCell® cardiomyocytes (Cellular Dynamics International) plated and allowed to fully mature and beat synchronously

**Assay Details**
Five concentrations in duplicate (dependent on customer requirements)
Single time point
Additional time points and washout (optional)

**Data Delivery**
Beat rate and number
Field potential duration
Amplitude
Conduction velocity (optional)

‘The recent applications of pluripotent stem cells and their derivatives in toxicology and drug research provide new alternatives to the standard routine tests performed by the industry and offer new strategies for chemical safety assessment.’

**Table 1**

Comparison of eCiphr<sup>®</sup> Cardio, hERG channel<sup>2,3,5,6</sup> and ex vivo/in vivo<sup>2,4,7,8,9,10</sup> results for compounds known for their effects on cardiac function.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Family</th>
<th>Number of Beats</th>
<th>Number of Beats (AC&lt;sub&gt;50&lt;/sub&gt;; µM)</th>
<th>Fast Na&lt;sup&gt;+&lt;/sup&gt; Slope (V/s)</th>
<th>Fast Na&lt;sup&gt;+&lt;/sup&gt; Slope (AC&lt;sub&gt;50&lt;/sub&gt;; µM)</th>
<th>Fast Na&lt;sup&gt;+&lt;/sup&gt; Amplitude (µV)</th>
<th>Fast Na&lt;sup&gt;+&lt;/sup&gt; Amplitude (AC&lt;sub&gt;50&lt;/sub&gt;; µM)</th>
<th>Field Potential Duration (ms)</th>
<th>Field Potential Duration (AC&lt;sub&gt;50&lt;/sub&gt;; µM)</th>
<th>In vivo or ex vivo Indication</th>
<th>Canine Purkinje Fibre Preparation (µM)</th>
<th>hERG Block (IC&lt;sub&gt;50&lt;/sub&gt;; µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Irreversible cyclooxygenase inhibitor</td>
<td>no change</td>
<td>&gt;100</td>
<td>no change</td>
<td>&gt;100</td>
<td>no change</td>
<td>&gt;100</td>
<td>no change</td>
<td>&gt;100</td>
<td>no prolongation</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Serotonin 5HT&lt;sub&gt;4&lt;/sub&gt; agonist</td>
<td>↓</td>
<td>0.083</td>
<td>↓</td>
<td>0.16</td>
<td>↓</td>
<td>0.16</td>
<td>↑</td>
<td>0.15</td>
<td>prolongation</td>
<td>0.1</td>
<td>0.03-0.1</td>
</tr>
<tr>
<td>FPL64176</td>
<td>L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channel activator</td>
<td>↓</td>
<td>0.039</td>
<td>↓</td>
<td>0.052</td>
<td>↓</td>
<td>0.053</td>
<td>↑</td>
<td>0.044</td>
<td>prolongation</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Isoproterenol</td>
<td>β-adrenergic receptor agonist</td>
<td>↑</td>
<td>0.18</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
<td>↓</td>
<td>0.17</td>
<td>shortening</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channel blocker</td>
<td>↑</td>
<td>0.34</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
<td>↓</td>
<td>0.12</td>
<td>no prolongation</td>
<td>&gt;10</td>
<td>not reported</td>
</tr>
<tr>
<td>Quinidine</td>
<td>HERG K&lt;sup&gt;+&lt;/sup&gt; channel blocker (class III antiarrhythmic)</td>
<td>↓</td>
<td>5.8</td>
<td>↓</td>
<td>5.0</td>
<td>↓</td>
<td>5.0</td>
<td>↑</td>
<td>2.7</td>
<td>prolongation</td>
<td>8.5</td>
<td>1</td>
</tr>
<tr>
<td>Sotalol</td>
<td>β-adrenergic receptor blocker</td>
<td>↓</td>
<td>44</td>
<td>↓</td>
<td>41</td>
<td>↓</td>
<td>42</td>
<td>↑</td>
<td>53</td>
<td>prolongation</td>
<td>100</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Verapamil</td>
<td>L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channel blocker</td>
<td>↑</td>
<td>0.34</td>
<td>↓</td>
<td>1.0</td>
<td>↓</td>
<td>1.0</td>
<td>↓</td>
<td>0.11</td>
<td>shortening</td>
<td>1</td>
<td>0.125</td>
</tr>
</tbody>
</table>

Red arrows point to the field potential duration (FPD, indicative of the QT interval duration). Verapamil clearly shortens FPD as compared to 0.1% DMSO (vehicle control). Note: In order to distinguish between the two traces, the voltage for verapamil is purposely shifted upward.

**Figure 1**

Raw traces for vehicle control (0.1 % DMSO) and test compound (verapamil).