**I. Dose-Limiting Toxicities**

- Nonclinical study data for pacrinib were reviewed to assess the concordance of the observed clinical pathologies and histopathologies associated with the JAK inhibitors.
- Results from the large animal studies were more predictive of clinical performance compared to results from the rodent studies.

**II. Myelosuppression**

- All the JAK inhibitors presented with reductions in red cell mass (red blood cells, hemoglobin, and/or hematocrit) and leukocyte populations.
- In the large animal studies, myelosuppressive effects were more pronounced with pacrinib and ruxolitinib.
- Results reflect the last hematologic sample time point prior to the end of the dosing phase of the study.

**III. Immunosuppression**

- Adverse effects of immunosuppression were primarily evident in the large animal studies.
- With pacrinib, one death of a large animal was possibly exacerbated by treatment-related immunosuppression.
- With ruxolitinib and tofacitinib, secondary infections were clearly treatment-related and prevalent in large numbers of dogs and monkeys, respectively.

**NONCLINICAL SUMMARY**

- For pacrinib, ruxolitinib, and tofacitinib, pivotal nonclinical studies were performed in one rodent model and one nonrodent large animal model. The goal of these studies was to identify any adverse effect level (NOAEL) if possible, and to characterize toxicities anticipated above that dose.
- Consistent with JAK inhibitors, the hematopoietic system (spleen, lymph nodes, thymus, bone marrow) was a toxicity target with all three JAK inhibitors. However, there were differences in the development of the myelosuppression and immunosuppression profiles.

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**Pivotal Nonclinical Toxicology Studies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Nonclinical Rodent Hematology in Pivotal Studies</th>
<th>Nonclinical Large Animal Hematology in Pivotal Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacrinib</td>
<td>Repeat dose toxicity studies for up to 6 mo. in the BALB/c mouse to 9 mo. in the Beagle dog</td>
<td>Repeat dose toxicity studies for up to 6 mo. in the Sprague-Dawley rat to 22 mo. in the cynomolgus monkey</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Repeat dose toxicity studies for up to 6 mo. in the Sprague-Dawley rat</td>
<td>Repeat dose toxicity studies for up to 6 mo. in the Sprague-Dawley rat</td>
</tr>
<tr>
<td>Tofacitinib</td>
<td>Repeat dose toxicity studies for up to 6 mo. in the Sprague-Dawley rat</td>
<td>Repeat dose toxicity studies for up to 6 mo. in the Sprague-Dawley rat</td>
</tr>
</tbody>
</table>