Clinical benefit of KTN0158 was observed in dogs with MCTs at -9. Two -10. In contrast to findings in dogs, IND enabling toxicology studies KTN0158 properties: Anti-C. Adverse events (AEs) were recorded and graded according to VCOG 21. Overall, nonclinical toxicology demonstrates a favorable safety 71. 9 -72. In Vitro 45 -74. CellTiter 21. Agonist Activity 45 -75. Hexosaminidase Release. 45 -76. In Vivo

KTN0158 Mechanism of Action and Activity

- KTN0158 inhibits Dog KIT Activation In Vitro and Decreases Mast Cell Numbers in Dog Skin In Vivo

- KTN0158 inhibits Dog KIT Activation In Vitro

Dose-dependent effect on mast cells in vivo (partial recovery at low dose)

KTN0158 Does Not Have Agonist Activity In Vitro

- No degradation in primary human mast cells in vitro at KTN0158 concentrations up to 1000 nM with or without IgE crosslinking
- KTN0158 did not induce KIT phosphorylation in cells expressing endogenous or exogenous KIT.

**Introduction**

- KTN0158 is a humanized anti-KIT IgG1 monoclonal antibody that is being developed as a potential therapy for cancer and mast cell-related diseases such as neuroinflammation type 1 (NF1)
- KTN0158 properties:
  - Binds canine, feline, human primate and human KIT with high affinity
  - Potent inhibitor of wild-type and some oncogenic variants of KIT
  - Modulates mast cell function and survival in vitro in dogs, cynomolgus monkeys and cats

**Methods**

- Human mast cells (primary human mast cells) were isolated from fresh peripheral blood mononuclear cells by standard methods and cultured in vitro in the presence of specific agonists.
- The human mast cell line SKM-1 was obtained from the American Type Culture Collection (ATCC) and maintained in RPMI 1640 media supplemented with 10% fetal bovine serum.
- Nonclinical studies were conducted in in vivo studies in canine, feline, non-human primate and cynomolgus monkeys.
- KTN0158 was administered intravenously.

**Clinical Study**

- No degradation in primary human mast cells in vitro at KTN0158 concentrations up to 1000 nM with or without IgE crosslinking
- KTN0158 did not induce KIT phosphorylation in cells expressing endogenous or exogenous KIT.

**Results**

- KTN0158 is a potential therapy for cancer and mast cell-related diseases due to its ability to inhibit KIT signaling.
- In vivo studies demonstrated the efficacy of KTN0158 in inhibiting mast cell activation and reducing mast cell numbers.

**Table: KTN0158 Mechanism of Action and Activity**

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Maximal Effect</th>
<th>Percentage Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>30</td>
<td>40%</td>
<td>90%</td>
</tr>
<tr>
<td>100</td>
<td>50%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Conclusions**

- Clinical benefit of KTN0158 was observed in dogs with MCTs at all dosing levels and in tumors with and without activating KIT mutations.
- Dogs with partial responses and 7 dogs with stable disease.
- Nonclinical toxicology studies in cynomolgus monkeys revealed no significant findings after repeat dosing of KTN0158 with the MTD established at 10 mg/kg.
- Overall, nonclinical toxicology demonstrates a favorable safety profile supporting planned clinical testing in human phase 1 studies in 2016 in GISTs and other solid tumors.

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