Nonclinical Safety Assessment of VX15/2503 – A Humanized IgG4 Monoclonal Antibody to SEMA4D

Vaccinex, Inc. Rochester, NY www.vaccinex.com

Introduction

• SEMA4D
  - Binds PLXNB1 with 1 nM affinity and CD27 with 300 nM affinity
  - Exists in both cellular and soluble forms
  - Is expressed abundantly on the surface of resting T cells and less strongly on B cells and APCs; it is upregulated upon cellular activation
  - Activates B lymphocytes and induces dendritic cell maturation for antigen presentation to T lymphocytes
  - Binding to PLXNB1 transduces NET promoting angiogenesis and stimulating growth of tumors
  - Is overexpressed in a variety of human tumors including head and neck, prostate, colon, and lung
  - Use of SHP1 to knockout the expression of SEMA4D reduced tumor growth and vascularization in mice
  - Therapeutic Rational for anti-SEMA4D Antibody: Neutralization of SEMA4D using a monoclonal antibody could inhibit tumor growth and invasion
  - VX15/2503 binds to 3 to 5 nM affinity to cellular and soluble SEMA4D and was selected for clinical development to treat patients with advanced solid malignancies
  - Additional research characterization data for SEM4D and VX15/2503 are presented as part of abstract #567

Species Selection

• Mouse analyses demonstrated that VX15/2503 exhibits 3 to 5 nM affinity for mouse, rat, marmoset, cynomolgus macaque, and human SEMA4D
• In vivo VX15/2503 blocked the binding of SEMA4D to PLXNB1 expressed on human and mouse cells
• Immunohistochemical analyses demonstrated reactivity of VX15/2503 in human, cynomolgus macaque, and rat lymphoid tissues
• A flow cytometric assay demonstrated dose dependent VX15/2503 binding to T cell associated SEMA4D on lymphocytes from rat, cynomolgus macaque, and human
• VX15/2503 binds with 3 to 5 nM affinity to soluble SEMA4D present in the sera of rats, cynomolgus macaques, and humans
• Normal healthy Sprague-Dawley rats were selected as an initial screening for anti-human SEMA4D antibodies in rats

Tissue Cross Reactivity

• A total of 36 human tissues were assessed for VX15/2503 reactivity (a subset is shown below)
• Human and cynomolgus macaque tissue reactivity profiles are similar
• Residual or infiltrating lymphoid tissues were reactive in many tissues, as expected
• Specific for the rat target tissue reactive with VX15/2503

Tissue Cross Reactivity

<table>
<thead>
<tr>
<th>Species</th>
<th>Brain</th>
<th>Gut</th>
<th>Heart</th>
<th>Kidney</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macaque</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Species</td>
<td>Skin</td>
<td>Spleen</td>
<td>Jejunum</td>
<td>Endometrium</td>
<td>Blood Cells</td>
</tr>
<tr>
<td>Human</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Macaque</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Abstract (Number 4578)

Toxicology Study Designs

• Appropriate acclimation and quarantine periods preceded study
• VX15/2503 was manufactured identically to cGMP processes except for the scale of production
• VX15/2503 was formulated at 1 mg/ml in 20 mM sodium acetate buffer pH 5.4 containing 130 mM NaCl and 0.02% polysorbate 80
• Single dose cynomolgus macaque, and rat and primate repeat dose study analyses were GLP compliant

Immunogenicity

• Anti-VX15/2503 antibody levels were determined by a modified bridging (ACE-ELISA) assay using mAb acid dissolution to increase drug tolerance
• Anti-VX15/2503 antibodies were typically detected within one to two weeks after injection
• Anti-VX15/2503 antibodies exerted only marginal effects on total exposure in low dose animals

Pharmacodynamics

• Animals were monitored for primary PD using a flow cytometric assay measuring the percentage of T cell associated SEMA4D (cSEMA4D) occupied by VX15/2503
• PD profiles were similar for rats and cynomolgus macaques
• cSEMA4D in rats and cynomolgus macaques administered 100 mg/kg VX15/2503 was saturated for a total of 120 and 141 days, respectively
• As expected with secreted antigens, uSEMA4D increased in cynomolgus macaques dosed with at least 0.1 mg/kg of VX15/2503

Clinical Observations and Pathology

• No adverse effects were noted in any study; NOAEL = 100 mg/kg (highest dose tested)
• Sporadic changes in serum globulin ratios detected in both repeat dose studies; these changes were attributed to the high serum globulin levels
• All treated rats in the repeat dose study showed a statistically significant increase in circulating NK cells (below); a similar statistically significant finding was not observed in primates
• NK cell levels in treated rats were similar to controls by the end of the recovery period; finding was not considered adverse due to absence of clinical correlates
• No test article related changes noted in clinical observations, physical or eye exams, body weights, ECG, vital, other clinical pathology parameters, organ weights or histopathology
• Clinical pathology evaluations of study animals were performed using standard equipment and practices

Summary

• VX15/2503 binds with high affinity to rat, cynomolgus macaque and human SEMA4D
• VX15/2503 was safe when administered to rats and cynomolgus macaques as five weekly IV doses up to 100 mg/kg/ dose on a biweekly dose level
• VX15/2503 exhibited prolonged T cell associated SEMA4D saturation
• These studies supported the initiation of a phase 1 clinical study to evaluate the safety and tolerability of VX15/2503 in patients with advanced solid tumors
• The animal studies described here also support completion of chronic toxicology studies in rats