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<table>
<thead>
<tr>
<th>Items</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product name</td>
<td>ASP2713 (Fc engineered anti-human Igβ Ab with high affinity for FcγRIIB)</td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td>Inhibition of B cell activation by Igβ and FcγRIIB cross-linking</td>
</tr>
<tr>
<td>Formulation</td>
<td>i.v.</td>
</tr>
<tr>
<td>Target Indication at Astellas</td>
<td>Autoimmune diseases (systemic lupus erythematosus)</td>
</tr>
<tr>
<td>Development Territory</td>
<td>Global</td>
</tr>
<tr>
<td>Latest development phase</td>
<td>CTA for P1</td>
</tr>
</tbody>
</table>
MECHANISM OF ACTION

ASP2713 is a Fc engineered anti-Igβ with high affinity for FcγRIIb.

Through the cross-linking of Igβ and FcγRIIb, ASP2713 can inhibit B cells in BCR signal dependent manner without destroying these important immune cells.

**Igβ**
- Signal transduction component of the B cell antigen receptor (BCR).
- Expression on B cell and plasmablast.
- Requirement for function of the BCR.

**FcγRIIB**
- Low affinity IgG receptor.
- Expression on B cell, plasmablast, plasma cell, mast cell, Mϕ, dendritic Cell.
- Having inhibitory ITIM motif in cytoplasmic region.
- Playing a role as negative feedback receptor.

ITIM: Immunoreceptor tyrosine-based inhibitory motif.
The targets cells of ASP2713 are not only B cells but also plasmablasts, CD20- antibody producing cells, therefore ASP2713 can broadly show suppressive effects compared to rituximab.
UNIQUENESS OF MOA OF ASP2713 IN COMPARISON TO EXISTING B CELL INHIBITORS

CDC: Complement-Dependent Cytotoxicity
ADCC: Antibody-Dependent Cell-mediated Cytotoxicity

anti-CD20, anti-CD19 Ab
ADCC and CDC
(requirement for effector cells and complement help)

ASP2713
Non-cytotoxic activity and Direct inhibition
(no requirement for effector cells and complement)

Blood 2010 116:3705-3714 modified
Healthy human primary B cells were treated with anti-IgM Ab in the presence of ASP2713.

B cell proliferation was measured by ATP quantification.

ASP2713 directly inhibited BCR-stimulated human B cell proliferation and did not require effector cells and complement.

**Graph:**

- **Y-axis:** % of response
- **X-axis:** Concentration (mol/L)
- **Legend:**
  - Control IgG1
  - ASP2713-IgG1 (native Fc)
  - ASP2713 (engineered Fc)

n=4, Mean ± SEM
ASP2713 showed superior suppressive effect on antibody production to rituximab.
ASP2713 did not show cytotoxic activity for B cells in vitro, although rituximab showed.

CDC: complement-dependent cytotoxicity, ADCC: Antibody-dependent cell-mediated cytotoxicity

### TOXICOLOGY STUDY LIST

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Species</th>
<th>Route</th>
<th>Dose (mg/kg)</th>
<th>GLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-dose toxicity</td>
<td>Cynomolgus monkey</td>
<td>iv</td>
<td>0, 3, 10, 100</td>
<td>No</td>
</tr>
<tr>
<td>Repeat-dose toxicity</td>
<td>Cynomolgus monkey</td>
<td>iv</td>
<td>0, 0.3, 1, 3, 30 (weekly)</td>
<td>Yes</td>
</tr>
<tr>
<td>Repeat-dose toxicity</td>
<td>Cynomolgus monkey</td>
<td>iv</td>
<td>0, 1, 3, 30 (weekly)</td>
<td>Yes</td>
</tr>
<tr>
<td>Local irritation</td>
<td>Cynomolgus monkey</td>
<td>sc</td>
<td>0, 3, 100</td>
<td>Yes</td>
</tr>
<tr>
<td>Tissue cross-reactivity</td>
<td>Human</td>
<td>in vitro</td>
<td>2, 10 µg/mL</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>Cynomolgus monkey</td>
<td>in vitro</td>
<td>0.5, 5 µg/mL</td>
<td>Yes</td>
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<tr>
<td>Cytokine release assay</td>
<td>Human</td>
<td>in vitro (aqueous)</td>
<td>0, 1, 10, 100, 1000 µg/mL</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in vitro (solid)</td>
<td>0, 1, 10, 100, 1000 µg/mL</td>
<td>No</td>
</tr>
</tbody>
</table>

- Safety studies have been performed in single species (cynomolgus monkeys) as ASP2713 did not cross-react either with the rat or mouse Igβ and cynomolgus monkeys are pharmacologically relevant species to ASP2713.

- No stand-alone safety pharmacology study was conducted, but relevant information was obtained during the 4-week repeated intravenous dose toxicity study in cynomolgus monkeys.
A novel B cell-targeting antibody (anti-Igβ & FcγRIIB cross-linking mAb)

Superior suppressive effect on antibody production to rituximab in a monkey model

No ADCC/CDC activity in vitro

No critical issues identified for further development
Patent covering ASP2713

  - Granted: Australia, China, European Patent (Austria, Belgium, France, Germany, Greece, Ireland, Italy, Netherlands, Poland, Portugal, Spain, Sweden, Switzerland, Turkey, United Kingdom), Hong Kong, Indonesia, Japan, Malaysia, Mexico, Philippines, Russian, Singapore, South Africa, Taiwan, Ukraine, USA
  - Pending: Argentina, Brazil, Canada, GCC, India, Israel, Korea, Thailand, Vietnam