ASP0659
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## PROGRAM CHARACTERISTICS

<table>
<thead>
<tr>
<th>Compound Name</th>
<th>ASP0659 hemifumarate</th>
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<tbody>
<tr>
<td>Mechanism of Action</td>
<td>alpha 7 nicotinic acetylcholine receptor positive allosteric modulator</td>
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<tr>
<td>Target Indication</td>
<td>Cognitive impairment associated with schizophrenia (CIAS)</td>
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<tr>
<td>Development Stage</td>
<td>Pre-IND</td>
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<td>Astellas’ original Target Product Profile (TPP)</td>
<td>To overcome the limitations of α7 nAChR agonists, a narrow therapeutic margin and development of tolerance</td>
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<tr>
<td>Product Concept</td>
<td>α7 nAChR PAM exhibits a superior and/or wider-range efficacy profile to α7 nAChR agonist without adverse effect.</td>
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<tr>
<td>TPP Concept</td>
<td>ASP0659 hemifumarate is expected to overcome the limitations of α7 nAChR agonists. ✓ Narrow therapeutic margin ✓ Development of tolerance</td>
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<tr>
<td>Research Hypothesis</td>
<td>In clinical studies, α7 nAChR agonists improved cognitive score and P50 sensory gating in schizophrenic patients. However, it is well known that α7 nAChRs desensitize very rapidly in response to high agonist concentrations both in vitro and in vivo, indicating that the agonists may be difficult to demonstrate consistent efficacy on cognition. We consider an α7 nAChR PAM, binding to the allosteric site of α7 nAChRs unlike the agonists, as a useful approach to overcome this shortcoming of α7 nAChR agonists.</td>
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**Alpha7 Nicotinic Acetylcholine Receptor (α7 nAChR)**

- A homomeric CNS-type nAChR, consisting of five α7 subunits
- Ligand-gated ion channel
  - Non-selective cation channel (High Ca$_{2+}$ permeability)
  - Rapid desensitization in response to ACh
  - Inverted U-shaped response
  - Heavy tobacco consumption and high nicotine dependence in schizophrenic patients are considered as form of self medication
  - Acute nicotine increases the amplitude of patients’ duration mismatch negativity
  - The 15q13-14 region of the genome coding for the α7 nAChR is linked to schizophrenia
  - Post mortem studies of schizophrenic patients show a marked decrease in the number of α7 nAChRs in the hippocampus and cortex.
  - Preliminary evidence (positive PoC data) suggests that α7 nAChR agonists can enhance cognition in schizophrenic patients.
α7 nAChR Agonist vs PAM

Gating Mechanism of α7 nAChR

- Open
- Inactivated
- High Affinity
- Activation
- Recovery
- Closed/Resting

α7 PAMs binding to allosteric site of the receptors can have a wider effective range than α7 agonists leading to rapid desensitization via the orthosteric site.
ASP0659 hemifumarate has better or comparable profiles compared with ASP6981 besilate

[Chemistry]
- ASP0659 hemifumarate has two different parts of structural distinction from ASP6981 besilate.

[Physicochemical properties]
- Hemifumarate form A01 was selected as K01 form.
- No special solubilized formulation will be needed for form A01 in clinical trials because favorable systemic exposure was observed in a dog absorption study.

[Pharmacology]
- ASP0659 hemifumarate is an orally active PAM of α7 nAChRs as well as ASP6981 besilate.
- ASP0659 hemifumarate significantly ameliorated cognitive impairment in the MK-801 Y-maze model (0.3, 1, 3 and 10 mg/kg) without the development of tolerance.
- ASP0659 hemifumarate significantly improved the methamphetamine-induced P50 sensory gating deficits in rats (1 and 10 mg/kg).

[ADME]
- No critical risks for development with low victim DDI risk.

[Safety pharmacology and toxicology]
- Lethal dose was 1000 mg/kg/day in 1-week oral repeated dose studies in both rats and cynomolgus monkeys. NOAELs were 3 and 30 mg/kg/day in rats and cynomolgus monkeys, respectively.
- QTc prolongations in ECG were observed at lethal dose in cynomolgus monkey 1-week study. The safety margin was 62-fold based on AUC.
- No other serious findings were noted.