



ASP6981
NON-CONFIDENTIAL SUMMARY



DISCLAIMER

This material includes forward-looking statements based on assumptions and beliefs in light of information currently available to the Astellas and subject to significant risks and uncertainties.

This material contains information on pharmaceuticals (including compounds in research or under development) and other matters. Notwithstanding the foregoing, Astellas makes no representations, warranties, assurances or guarantees of any kind or nature whatsoever, whether expressed or implied, regarding the information in the materials (including, without limitation, no representations, warranties, assurances or guarantees as to the accuracy, sufficiency or completeness of any information, as to whether Astellas has rights to any such information or pharmaceuticals/compounds, as to whether any third party has or does not have any rights to any of such information or pharmaceuticals/compounds, as to the safety, efficacy, or effectiveness of any preparations described in this material, as to the regulatory status of or potential for regulatory agency action regarding any pharmaceuticals/compounds described in this material, or as to any uses, including unapproved uses, of any such preparations in any fashion). This material does not provide medical advice of any kind.

Astellas undertakes no obligation or duty to change, remove, add, clarify, correct or update any information in the materials at any time.



ASP6981 CHARACTERISTICS

- Mechanism of Action: $\alpha 7$ nicotinic acetylcholine receptor positive allosteric modulator ($\alpha 7$ nAChR PAM)
- Target Indication: Cognitive impairment associated with schizophrenia (CIAS)
- Development Regions: Global
- Formulation: Tablet (Oral capsule up to Phase 2a)
- Estimated patent term: 2036 + α (α = max 5 years)
- Development phase: Pre-clinical

ASTELLAS' TARGET PRODUCT PROFILE (1)

Compound name	ASP6981
Class/MoA	α 7-nicotinic acetylcholine receptor positive allosteric modulator
Indication	ASP6981 is indicated for the improvement of cognitive impairment associated with schizophrenia
Target Patient Segment	<ul style="list-style-type: none">• Diagnosed prevalent schizophrenia patients• Majority of schizophrenia patients are affected by cognitive impairment
Key competitors	None (there is no approved drug indicated for CIAS)
Target efficacy	ASP6981 shows statistically significant and clinically meaningful efficacy both cognition and functional measurement in well-controlled studies of 6-12 months duration as primary endpoints: <ul style="list-style-type: none">• Cognition measure: Statistically significant improvement, with an effect size of at least 0.35, over placebo in the MATRICS composite score (MCCB)• Functional measure: Statistically significant improvement over placebo in the UPSA total score

ASTELLAS' TARGET PRODUCT PROFILE (2)

Target efficacy	<p>Secondary endpoints: Additional secondary endpoints are included to confirm that psychotic symptom/motor disturbance do not become worse.</p> <p>The onset of efficacy is expected to be within 12 weeks</p>
Target safety	<p>No clinically important or significant increase in AE burden or reduction in antipsychotic efficacy</p>
Dosing and administration	<ul style="list-style-type: none">• Oral administration, qd or bid• Tablet: estimated daily dose is 100 mg/day
Others	<p>No clinically significant DDIs with commonly used concomitant medications, especially antipsychotics, leading to restriction/dose adjustment</p>

COGNITIVE IMPAIRMENT IN SCHIZOPHRENIA

- Cognitive impairment associated with schizophrenia appears to be a core component to this disease as reflected in three key features:
 - ✓ Cognitive impairment is present in those adolescents thought to be at risk for developing schizophrenia prior to the first psychotic episode in the 2nd or 3rd decade of life.
 - ✓ Cognitive impairment is a lifelong symptom
 - ✓ Cognitive impairment appears related to unfavorable outcomes in education, work and social relationships.
- Cognitive impairment in schizophrenia reflects dysfunction across a range of cognitive domains including attention, working memory, executive function, and episodic memory.
- Cognitive impairment is independent of the severity of positive symptoms and is only modestly correlated with negative symptoms.
- Current antipsychotic treatments appear to have little if any impact on the cognitive impairment associated with schizophrenia.

SUMMARY OF NON-CLINICAL DATA

- Pharmacological dose responses of ASP6981 in animal models for cognition (both the Y-maze and P50 SG models) appeared to be sigmoidal, and PK and PD appeared to be closely linked.
- No serious toxicological concerns were identified in the safety pharmacology or repeated dose (4-week) toxicity studies.
- The major findings in ASP6981 were effects on CNS, erythrocytic parameters, skeletal muscle, liver, GI and testis.
 - CNS, erythrocytic parameters, skeletal muscle, liver and GI:
 - ✓ Although safety margins are relatively small, all findings were not considered seriously adverse, are monitorable and reversible.
 - Testis:
 - ✓ The finding was very slight to slight in severity, and its reversibility was confirmed.
- No genotoxic or phototoxic potential was noted.
- Some findings (external malformations) were noted in the preliminary embryo-fetal development study in rats. It is unclear if they are drug-related or incidental changes. To clarify the potential of teratogenicity, the definitive embryo-fetal development study in rats is ongoing now.

ROLE OF A7 NICOTINIC ACETYLCHOLINE IN CIAS

- The 15q13-14 region of the genome coding for the $\alpha 7$ nAChR is linked to schizophrenia
- Post mortem studies of schizophrenic patients show a marked decrease in the number of $\alpha 7$ nAChRs in the hippocampus and cortex.
- Localization of hippocampal nAChRs Involved in memory pathways
- Heavy tobacco consumption and high nicotine dependence in schizophrenic patients are considered as form of self medication
- Clinical Evidence:
 - ✓ Preliminary evidence (positive PoC data from multiple sponsors) suggests that $\alpha 7$ nAChR agonists can enhance cognition in schizophrenic patients.
 - ✓ Encenicline, an $\alpha 7$ nAChR partial agonist, demonstrated positive effects in Phase-2b trial in patients with CIAS, though it failed Phase-3 trial possibly also due to factors unrelated to the MoA.

WHY ASP6981 AN $\alpha 7$ NACHR PAM FOR CIAS IS EXCITING

$\alpha 7$ nAChR activation is considered an attractive target for CIAS by KOLs as:

- the functional properties & anatomical localization of the $\alpha 7$ nAChR makes it well suited to modulate cognitive function.
- $\alpha 7$ nAChR agonists/PAMs improve learning, memory, and attentional function in variety of animal models, and procognitive effects of $\alpha 7$ nAChR agonists have been demonstrated in patients with schizophrenia.
- However, the $\alpha 7$ nAChR desensitizes rapidly and this has been a major concern in the development of $\alpha 7$ nAChR agonists as putative drugs.
- An $\alpha 7$ nAChR PAM binds to allosteric site of the receptor & can have a wider effective range than $\alpha 7$ agonist.
- $\alpha 7$ PAM such as ASP6981 could circumvent the desensitization and provide a wider exposure window for efficacy.

