ASP4345
NON-CONFIDENTIAL SUMMARY

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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.

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ROLE OF DOPAMINE IN CIAS

- Dopamine is one of the most important neurotransmitters in the central nervous system.
- Dopamine receptors are classified into either D1-class (D1 and D5 receptors) or D2-class (D2, D3, and D4 receptors).
- D1 receptors are expressed at a high level of density in the dopamine rich area of the forebrain and play a crucial role in a variety of cognitive functions.
- One of the therapeutic targets for CIAS is the activation of D1 receptors.
- The hyperactivity of dopamine in subcortical structures is thought to be associated with positive symptom, whereas D1 receptor hypoactivity in the frontal cortical area has been suggested to attribute to the negative symptom and impaired cognitive function. D1 receptors in frontal cortex are reported to be involved in the working memory expression.
- These findings indicate that the stimulation of D1 receptor is a promising target for improving CIAS. However, no D1 receptor agonists have been successful as drug candidates for CIAS because of their powerful hypotensive effect.

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WHAT IS ASP4345 AND WHY IS IT EXCITING

- CIAS is important and a valuable opportunity.
- Dopamine D1 receptor agonist activity is an attractive target, but limited by cardiovascular hypotensive effects.
- ASP4345 is a D1 PAM
- preclinical evidence of in vivo and in vitro D1 PAM effects
- Efficacy in animal models without hypotensive effects

SUMMARY OF NON-CLINICAL DATA

- The clinical dose of ASP4345 was estimated to be 11.5-1085 mg/day
- Toxicological targets are the gastrointestinal tract and liver. In addition, decreased blood pH and increased blood Cl were observed. All findings are reversible and considered to be monitorable in clinical trials. There are no genotoxic, teratogenic or phototoxic potential. There were no serious toxicological findings that may hamper the P1 clinical trial of ASP4345.
- No effect on blood pressure have been observed so far.

ASTELLAS' TARGET PRODUCT PROFILE

Class/MoA	Dopamine D1 receptor positive allosteric modulator
Indication	ASP4345 is indicated for the improvement of cognitive impairment associated with schizophrenia
Target Patient Segment	• 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	ASP4345 shows statistically significant and clinically meaningful efficacy both cognition and functional measurement in well-controlled studies of 6-12 months duration as primary endpoints: • 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 Secondary endpoints: Additional secondary endpoints are included to confirm that psychotic symptom/motor disturbance do not become worse. The onset of efficacy is expected to be within 12 weeks
Target safety	No clinically important or significant increase in AE burden or reduction in antipsychotic efficacy
Dosing and administration	• Oral administration, qd or bid • Tablet: estimated daily dose is 11.5 - 57 mg/day
Others	No clinically significant DDIs with commonly used concomitant medications, especially antipsychotics, leading to restriction/dose adjustment

ASTELLAS' EARLY CLINICAL DEVELOPMENT STRATEGY

- Manage risks and get to proof of concept as quickly as possible.
- Engage KOLs to manage BM selection, translation challenges and data interpretation.
- Use stable schizophrenia patients in Phase 1, and genotype population for COMT polymorphism.

SAD study, CL-0001:

- Evaluation of initial safety/tolerability/PK after single rising doses in HVs.
- Measurement of CSF exposure and ASSR assessment will be considered if translatable preclinical data becomes available.

MAD study, CL-0002:

- Evaluation of safety/tolerability/PK after rising repeat dosing in stable schizophrenic patients.
- Evaluation of a panel of biomarkers (Electrophysiology and cognition measures) which are expected to respond with drug administration.

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COMPLETED CLINICAL STUDIES THUS FAR

4345-CL-0001:
A Phase 1 Single Ascending Oral Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of ASP4345 in Healthy Male and Female Subjects, Including Assessments of Pharmacokinetics in Cerebrospinal Fluid, Neurophysiological Biomarkers and Evaluation of Food Effect

4345-CL-0002:
A Phase 1 Multiple Ascending Oral Dose Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ASP4345 in Patients with Schizophrenia

4345-CL-0015:
A Phase 2a, Randomized, Double-Blind, Placebo-Controlled, Parallel-group Study to Assess the Safety and Efficacy of ASP4345 as Add-on Treatment for Cognitive Impairment in Subjects with Schizophrenia on Stable Doses of Antipsychotic Medication

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