ABL301 is a novel bispecific antibody therapeutic against synucleinopathy. Aggregated α-synuclein (α-Syn) has been known to be an important pathologic factor to Parkinson’s disease (PD). ABL301 is developed for selective binding to aggregated α-Syn and better blood-brain barrier (BBB) penetration. The purpose of this study is to show improved efficacy of ABL301 by selectively targeting aggregated α-Syn with enhanced BBB penetration using in vitro and in vivo model systems.

### Objectives

- **ABL301** is a novel blood-brain barrier-crossing bispecific antibody targeting aggregated α-synuclein (ABL301) attenuates α-synucleinopathy

### Results

- **Anti-α-Syn IgG of ABL301 recognized α-Syn inclusions in post-mortem human PD & MSA brains**
- **Anti-α-Syn IgG of ABL301 reduced α-Syn transfer to GFP+ dopaminergic neurons derived from iPSC from a PD patient carrying A35T mutation**

### ABL301 showed 10-fold higher BBB penetration than mAb

- Serum half life: mAb: 124 h and bsAb (ABL301): 118 h
- Peak at 24h and CNS retention up to 168 hrs post-treatment
- Brain and CSF AUC of bsAb is 8-9 fold higher than mAb

### ABL301 reduced Lowy body-like inclusions after 90 days post injection

- (A) Representative p-α-Syn immunohistochemistry images in the cerebral cortex (CC) and striatum (STR).
- (B) Quantifications of the number of p-α-Syn inclusions.
- (C) Distribution of LB/LN-like pathology in the CNS of α-syn PFF-injected hemisphere.
- (D) Representative Western blots illustrating the differences in band intensities of p-α-Syn in the cerebral cortex of α-syn PFF-injected hemisphere.

- (E) Quantifications of p-α-Syn expressions.

- ABL301 protected dopaminergic tracts/cells from degeneration induced by α-Syn PFF

- (A) Representative TH immunohistochemistry images of SNpc. Arrows indicate TH-positive neurons in SNpc.
- (B) Quantifications of the number of TH-positive neurons in SNpc.
- (C) Percentages of the number of TH-positive neurons in ipsilateral SNpc compared to contralateral SNpc.
- (D) Representative TH immunostaining images of the striatum of α-syn PFF-injected hemisphere.
- (E) Quantifications of TH-immunopositive fiber densities in ipsilateral striatum.

### ABL301 improved behavioral deficits of mouse models with synucleinopathies

- Effect of ABL301 on behavioral deficits of α-Syn PFF-injected mice (A) and MBP human α-Syn tg mice (B).
- Assessments of movement (balance and motor coordination) deficits measured by the rotarod test.

### Conclusion

- ABL301 induces a significant reduction in p-α-Syn burden in α-Syn PFF-injected mice.
- ABL301 shows apparent protection against degeneration of dopaminergic system in α-Syn PFF-injected mice.
- ABL301 improves motor impairment in α-Syn PFF-injected mice and MBP-α-Syn tg mice.
- ABL301 is developed as a best-in-class antibody therapeutics for the treatment of α-synucleinopathy by aggregate-selective targeting and improved BBB penetration.