1101 ASKG315 – AN IL-15 PRODRUG WITH ANTIBODY-LIKE PK, ENHANCED SAFETY AND EXPANDED THERAPEUTIC WINDOW

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Background AskGene has established a proprietary cytokine prodrug platform (Smartkine®) to achieve its overarching objective of modulating immune reactions at a disease site in a selective and controlled manner. Cytokines are potent molecules, yet their broad application as therapeutics has been hampered due to short PK, severe systemic toxicity, and narrow therapeutic window. To improve the therapeutic potential of cytokines, AskGene has developed several cytokine prodrugs using its proprietary SmartKine® platform. To our knowledge, ASKG315 is the first IL-15 prodrug moving into clinical development.

Methods The in vitro activities of ASKG315 were evaluated using reporter assay and PBMC-based assays. The anti-tumor activities were tested in human PBMC-engrafted tumor xenograft models. The PK/PD properties and safety profiles of ASKG315 were assessed in non-human primates (NHPs) following three IV injections every two weeks.

Results ASKG315 showed minimal activity prior to protease-dependent activation and significantly enhanced activity after protease-dependent activation in vitro. It selectively stimulated NK cells and CD8+ T cells in vitro. In in vivo efficacy studies, ASKG315 at 0.3 mg/kg showed similar potency and better safety compared to a reference IL-15 molecule (unmasked) at 0.5 mg/kg, suggesting that ASKG315 had an expanded therapeutic window. These results also showed that, compared to the reference molecule, ASKG315 had similar or higher immune stimulation in the tumor while having significantly reduced immune stimulation in the periphery. In NHPs, ASKG315 demonstrated prolonged and antibody-like PK profiles. It selectively induced proliferation of NK cells and CD8+ T cells while showing minimal effect on CD4+ T cells in vivo. In addition, ASKG315 was well tolerated at the highest dosage tested in NHPs, with no cytokine release syndrome (CRS) and minimal immune reaction at injection sites.

Conclusions Activated ASKG315 showed selective stimulation for NK cells and CD8+ T cells in vitro and in vivo. ASKG315 in vivo showed less periphery immune activation and higher anti-tumor activity compared to the reference molecule. In addition, it had extended antibody-like PK in NHPs and was well tolerated at the highest dosage tested in the GLP safety study. It also showed a significantly expanded therapeutic window. A first-in-human (FIH) study for ASKG315 is expected to start in the second half of 2022.

Ethics Approval The uses of the animals in the in vivo studies were approved by the ethics committees of the CROs who performed the studies.

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