

**Abstract N°: 4711****Characterization of ORKA-001, a Novel Extended Half-life Monoclonal Antibody Targeting IL-23 for the Treatment of Psoriasis**

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Introduction & Objectives:

Interleukin 23 (IL-23) is a proinflammatory cytokine that helps to maintain and activate T helper 17 (Th17) cells, the primary pathogenic cells in psoriasis. IL-23 plays a key role in the pathogenesis of psoriasis, as indicated by the association between the disease and mutations in components of the IL-23 signaling pathway, such as *IL23R*. Antagonism of the p19 subunit of IL-23 (IL-23p19) has proven to have robust efficacy and a favorable safety profile in the treatment of psoriasis. ORKA-001 is a novel, extended half-life, humanized IgG1 monoclonal antibody that binds IL-23p19. ORKA-001 has been engineered to have optimized properties with the aim of delivering an enhanced clinical profile compared to current treatments for psoriasis.

Materials & Methods:

ORKA-001 was evaluated in multiple *in vitro* and *ex vivo* assays in comparison to two benchmark antibodies that target IL-23p19: risankizumab (RIS) and guselkumab (GUS). Binding affinity to IL-23 was determined by surface plasmon resonance (SPR). Antagonism of human IL-23 signaling was evaluated via assays measuring STAT3 activity in cell lines. Inhibition of IL-23-induced IL-17 secretion was assessed using *in vitro* cellular assays, including in human peripheral blood mononuclear cells (PBMC). Half-life extension was measured via pharmacokinetic (PK) analysis in cynomolgus monkeys dosed with a single bolus of ORKA-001.

Results:

ORKA-001 binds specifically to human IL-23 with an affinity below 20pM. It potently inhibits STAT3 activity in cell lines and IL-17 secretion in IL-23-stimulated human PBMC. IL-23 binding affinity and functional potencies for IL-23 antagonism are comparable to or better than those of RIS and GUS. The half-life of ORKA-001 is significantly extended in cynomolgus monkeys compared to both RIS and GUS. Based on allometric scaling of the clearance of ORKA-001 observed in this study, predictive simulations of ORKA-001 PK in humans suggest that subcutaneous maintenance dosing every six to twelve months could be achieved while maintaining high antibody exposures.

Conclusion:

ORKA-001 exhibits high selectivity and affinity for IL-23 *in vitro*, potent inhibition of downstream cellular signaling *ex vivo*, and an extended half-life in non-human primates compared to RIS and GUS. Both affinity and antibody exposure have been shown to have a positive correlation with efficacy in psoriasis, and ORKA-001 has the potential to exceed RIS and GUS on both metrics while requiring significantly fewer doses per year. In total, these data provide preclinical evidence of ORKA-001's clinical potential to improve upon currently available therapies for psoriasis. Clinical studies are warranted to demonstrate this potential.

