Characterization of ORKA-001, a Novel Extended Half-life Monoclonal Antibody Targeting IL-23 for the Treatment of Psoriasis

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P3283

Introduction

- Oruka Therapeutics is advancing a portfolio of potentially best-in-class antibodies that target the core mechanisms underlying plaque psoriasis and other dermatologic and inflammatory diseases.
- The pipeline consists of molecules developed by Paragon Therapeutics, which employs a breadth of protein engineering technologies to discover and optimize biologics targeting established mechanisms.
- 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[1]. 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[2].
- ORKA-001 is a novel, highly specific, humanized IgG1 monoclonal antibody that potently inhibits IL-23p19.
- ORKA-001 is designed to have higher and longer antibody exposure due to half-life extension through YTE substitution, a validated Fc modification method (Figure 2).
- Since both affinity and antibody exposure of IL-23p19 inhibitors have been shown to have a positive correlation with efficacy in psoriasis[3,4], ORKA-001 has the potential to deliver an enhanced clinical profile compared to current treatments for psoriasis.

Disclosures

- Byron Kwan, Mohammad Murshid Alam, Jacob Milligan, Soraia Oliveira, Jason Oh, and Hussam Shaheen are employees and stockholders of Paragon Therapeutics.
- Christopher Finch, Joana Goncalves, and Laura Sandler are employees and stockholders of Oruka Therapeutics.

Figure 1: ORKA-001: A novel highly specific extended half-life monoclonal antibody targeting IL-23p19

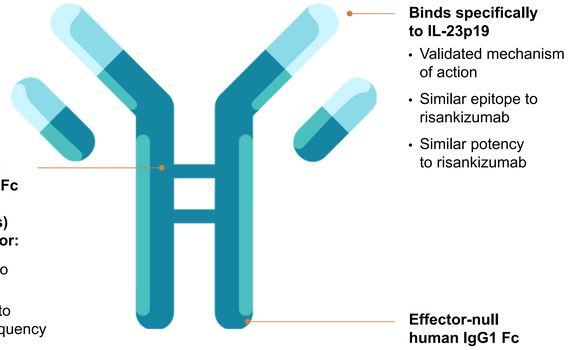


Figure 2: 'YTE' substitution increases the pH-dependent affinity of the Fc region for FcRn, extending antibody half-life

- M252Y/S254T/T256E ("YTE") amino acid substitutions to the Fc region of antibodies increases the pH-dependent binding affinity to FcRn.
- YTE substitution results in increased antibody recycling, causing less lysosomal degradation and thus a prolonged half-life of the antibody.

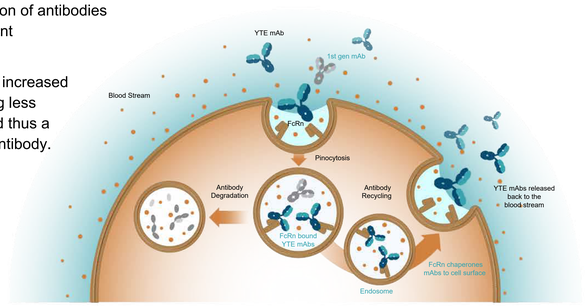


Figure adapted from Apogee Therapeutics

Methods

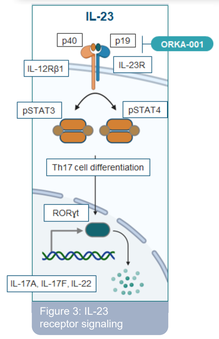


Figure 3: IL-23 receptor signaling

- 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 (Figure 3).
- Inhibition of IL-23-induced IL-17A secretion was assessed using in vitro cellular assays in human peripheral blood mononuclear cells (PBMC) and mouse splenocytes.
- Half-life extension was measured via pharmacokinetic (PK) analysis in cynomolgus monkeys dosed with a single bolus of ORKA-001.

Created from: Moschen, et al. Nat Rev Gastroenterol Hepatol. (2019); Verstockt, et al. Nat Rev Gastroenterol Hepatol. (2023)

RESULTS

Figure 4: ORKA-001 binds IL-23p19 at a similar epitope as risankizumab with similar affinity

- ORKA-001 and RIS demonstrate comparable high affinity for IL-23p19 (K_D <5 pM).
- Cryo-EM structural analysis demonstrates that ORKA-001 has a nearly identical epitope as RIS (Figure 4).

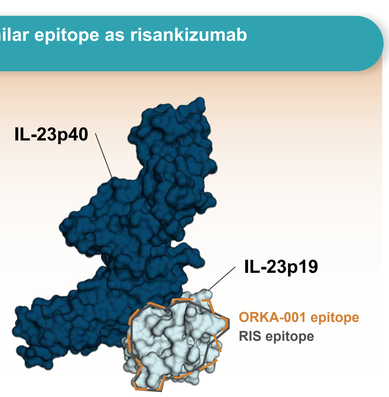
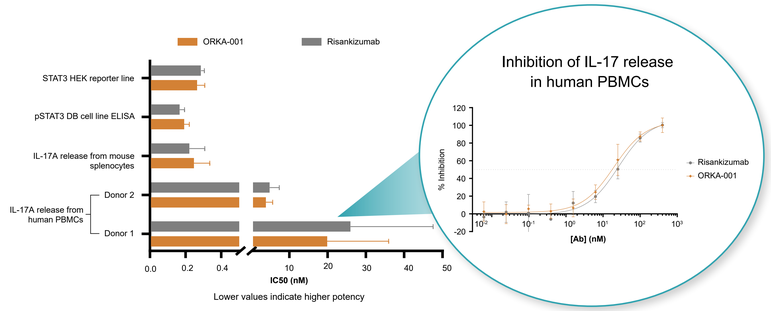


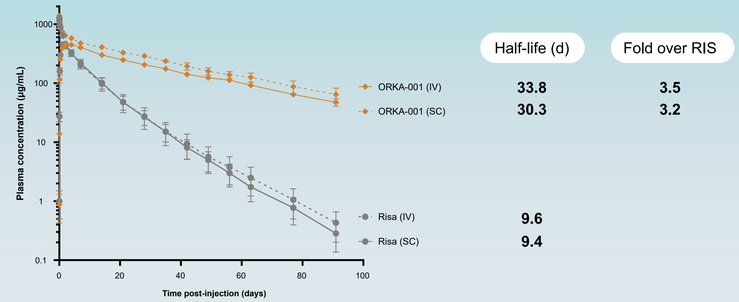
Figure 5: ORKA-001 shows equal or better potency to RIS across a variety of in vitro assays

- ORKA-001 potently inhibited STAT3 activity in cell lines and IL-17A secretion in IL-23-stimulated human PBMC and mouse splenocytes (Figure 5).
- ORKA-001 functional potencies for IL-23 antagonism were comparable to or better than those of RIS (Figure 5) and GUS (not shown).



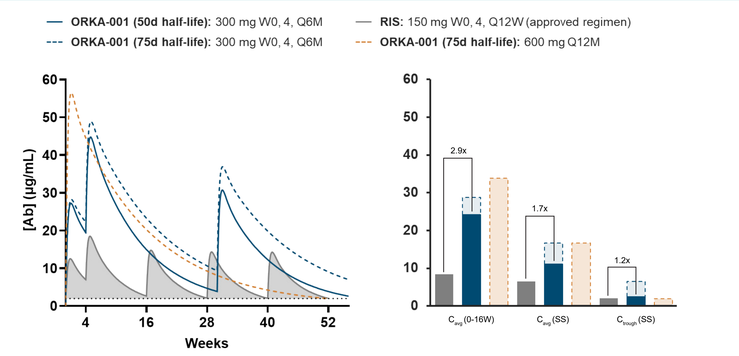
Lower values indicate higher potency

Figure 6: ORKA-001 demonstrates an extended half-life in non-human primates (NHP)



The half-life of ORKA-001 was significantly extended in cynomolgus monkeys compared to RIS (Figure 6). Obvious timepoints affected by anti-drug antibodies due to cross-species reactivity were excluded from analysis in accordance with standard practice (N=1 in ORKA-001 SC group).

Figure 7: Predictive simulations of ORKA-001 PK in humans suggest potential for dosing every six to twelve months



- Predictive simulations of ORKA-001 PK in humans suggest that a half-life of ~50 days would enable subcutaneous maintenance dosing every 6 months while a half-life of ~75 days would enable subcutaneous maintenance dosing every 12 months while maintaining trough antibody concentrations equal to or above risankizumab (Figure 7).
- YTE-modified antibodies on average have a human half-life that equals approximately 2-4x the NHP half-life. The half-life for ORKA-001 observed in NHPs (Figure 6) therefore supports the potential to achieve at least Q6M and even Q12M dosing.
- All half-life and dosing scenarios result in higher average exposures for ORKA-001 compared to risankizumab, which has the potential to lead to higher efficacy based on published results with risankizumab[3,5]

Conclusions

- ORKA-001 exhibits high affinity and selectivity for IL-23p19 in vitro and potent inhibition of downstream cellular signaling.
- ORKA-001 demonstrated a half-life of over 30 days in non-human primates, which exceeds that of risankizumab by over 3-fold.
- ORKA-001 has the potential to match or exceed RIS and GUS on potency while requiring only twice or once per year dosing.
- These data provide preclinical evidence of ORKA-001's clinical potential to meaningfully improve upon currently available therapies for psoriasis.

References: 1. Harrington et al. 2005, Nat Immunol; 2. Ruggiero et al. 2023, Immunol Res; 3. Blauvelt et al. Presented at AAD 2024, San Diego, CA; 4. Daniele et al. 2024 JID Innov; 5. Khatri et al. 2019, J Clin Pharmacol.

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