

# Characterization of ORKA-002, a Novel Extended Half-life Monoclonal Antibody Targeting IL-17A/F for the Treatment of Psoriasis and Other Indications

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## 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.
- The IL-17 family of cytokines includes 6 members (IL-17A to IL-17F). Both IL-17A and IL-17F are key drivers in the pathogenesis of psoriatic disease, being highly overexpressed in psoriatic plaques and the inflamed synovium of patients with psoriatic arthritis.
- Recently, a biologic targeting both IL-17A and IL-17F, bimekizumab, has demonstrated high efficacy that exceeds therapies targeting IL-17A only.
- ORKA-002 is a novel, extended half-life, humanized monoclonal antibody that potently inhibits IL-17A and IL-17F.
- ORKA-002 has been engineered to have optimized properties with the aim of delivering an enhanced clinical profile compared to currently available treatments for psoriasis and other inflammatory diseases

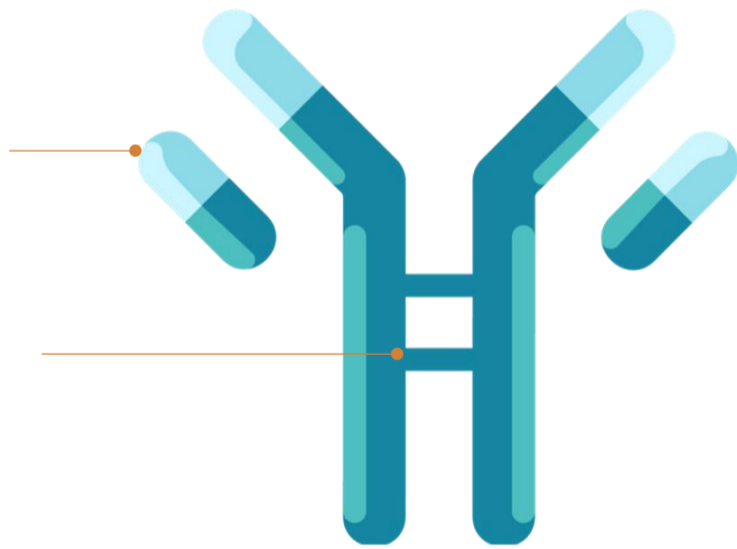
## Disclosures

- Byron Kwan, Daniel Rios, Joana Ministro, Jacob Milligan, Ghassan Fayad, Jason Oh, and Hussam Shaheen are employees and stockholders of Paragon Therapeutics.
- Christopher Finch, Eugenia Levi, and Joseph Senn are employees and of Oruka Therapeutics.
- Christopher Finch, Eugenia Levi, Andrew Blauvelt and Joseph Senn are stockholder of Oruka Therapeutics.

Reference: 1. Prinz I, et. al. Interleukin-17 cytokines: Effectors and targets in psoriasis-A breakthrough in understanding and treatment. J Exp Med. 2020 Jan 6;217(1):e20191397.

## Figure 1: ORKA-002: A novel highly specific extended half-life monoclonal antibody targeting IL-17A and IL-17F

- Binds specifically to IL-17A and IL-17F to prevent homodimer and heterodimer signaling, a validated mechanism of action
- Half-life extension through validated Fc modification (YTE substitutions) creates potential for reduced dosing frequency



## 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

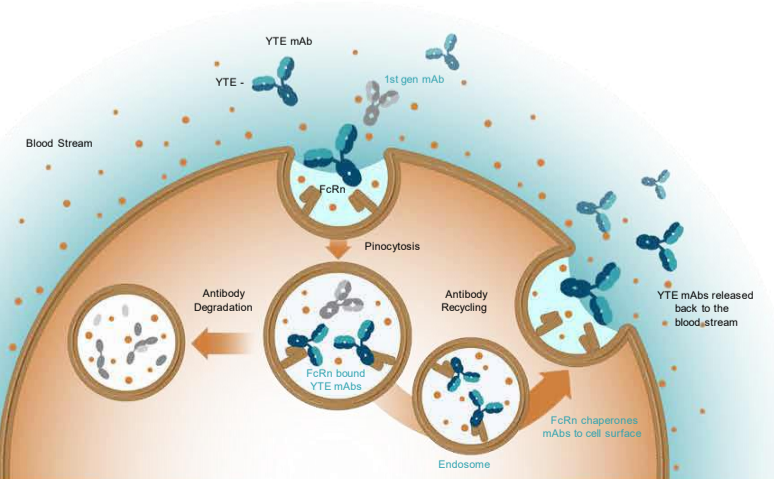


Figure adapted from Apogee Therapeutics

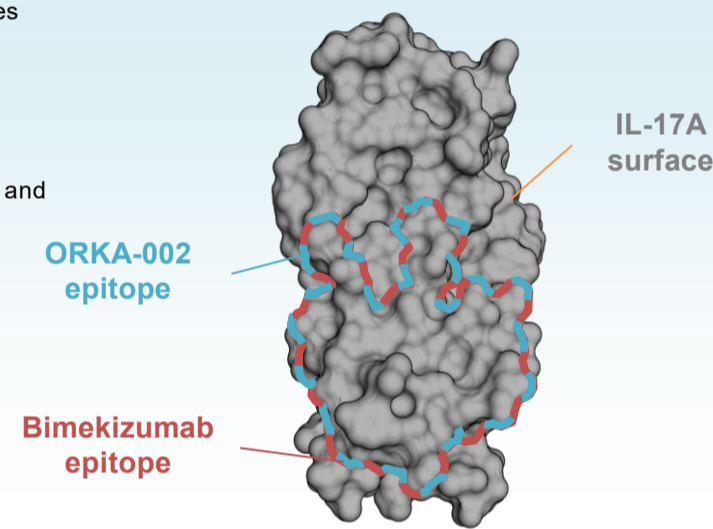
## Methods

- ORKA-002 was evaluated in multiple in vitro and ex vivo assays in comparison to the benchmark antibody that targets IL-17A and IL-17F: bimekizumab (BIME).
- Binding affinity to IL-17A and IL-17F was determined by surface plasmon resonance (SPR).
- Antagonism of IL-17A and IL-17F signaling was assessed NFκB activation assays in reporter cell lines.
- Inhibition of IL-17A-induced or IL-17F-induced IL-6 secretion was measured in vitro using normal human dermal fibroblasts.
- Half-life extension was evaluated via pharmacokinetic (PK) analysis in cynomolgus monkeys following a single bolus dose of ORKA-002.

## RESULTS

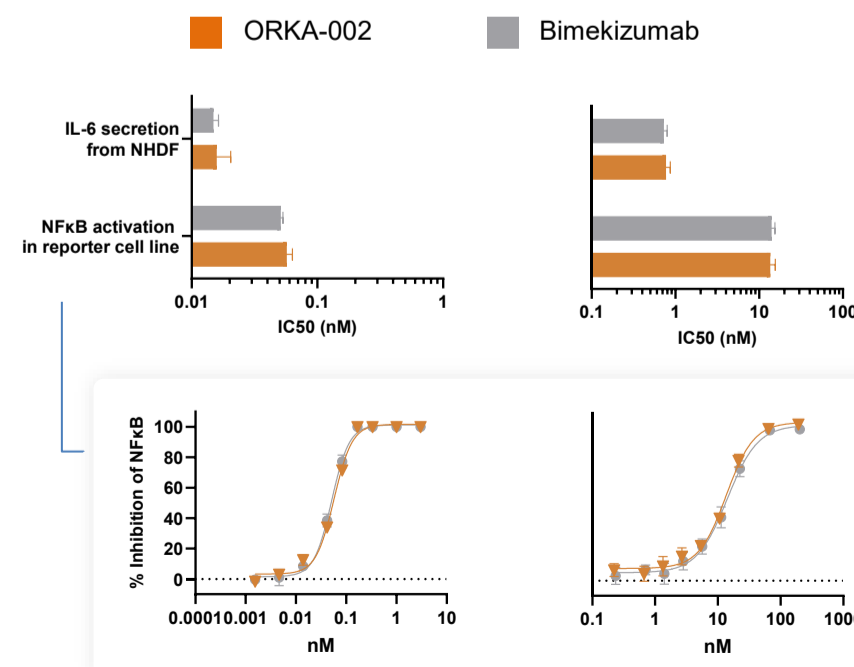
### Figure 3: ORKA-002 binds IL-17A and F at a similar epitope as bimekizumab with similar affinity

- Cryo-EM structural analysis demonstrates that ORKA-002 has a nearly identical epitope as bimekizumab for both IL-17A (above) and IL-17F (not shown)
- ORKA-002 and bimekizumab have comparable picomolar affinity for IL-17A and IL-17F by surface plasmon resonance (SPR)



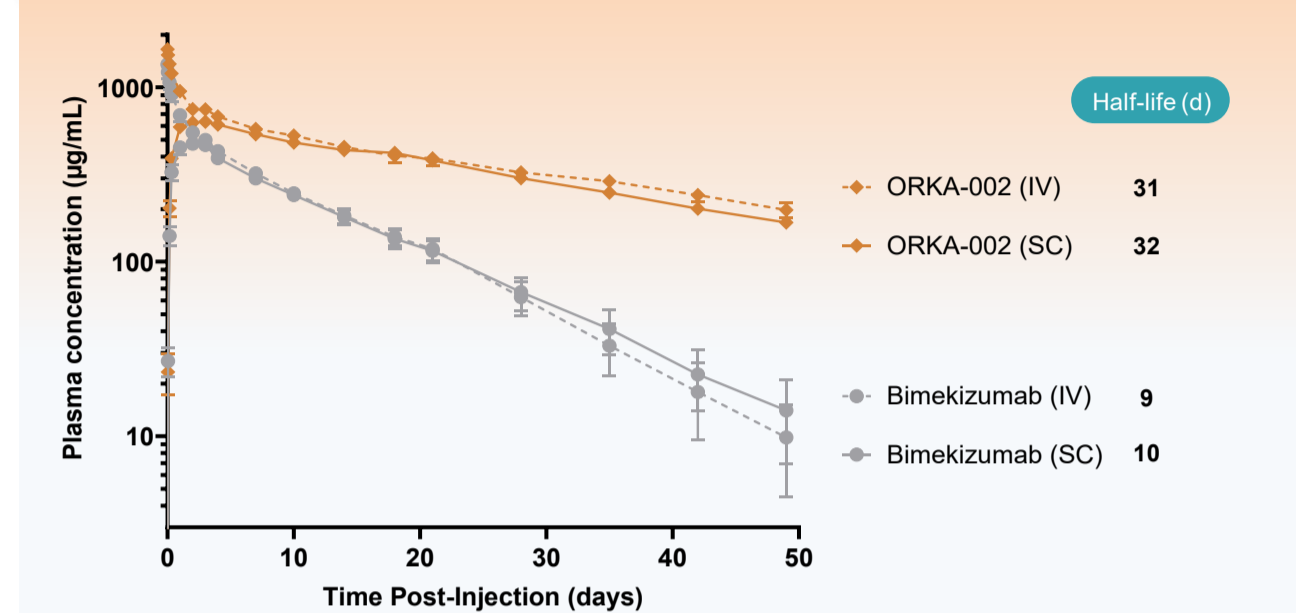
### Figure 4: ORKA-002 shows similar potency to bimekizumab across multiple in vitro assays

- ORKA-002 bound specifically to human IL-17A and IL-17F with high affinity.
- IL-17A and IL-17F binding affinity and functional potencies for IL-17A and IL-17F antagonism were comparable to BIME (Figure 4).



Abbreviations: NHDF, normal human dermal fibroblasts

### Figure 5: ORKA-002 demonstrates an extended half-life in non-human primates (NHP)

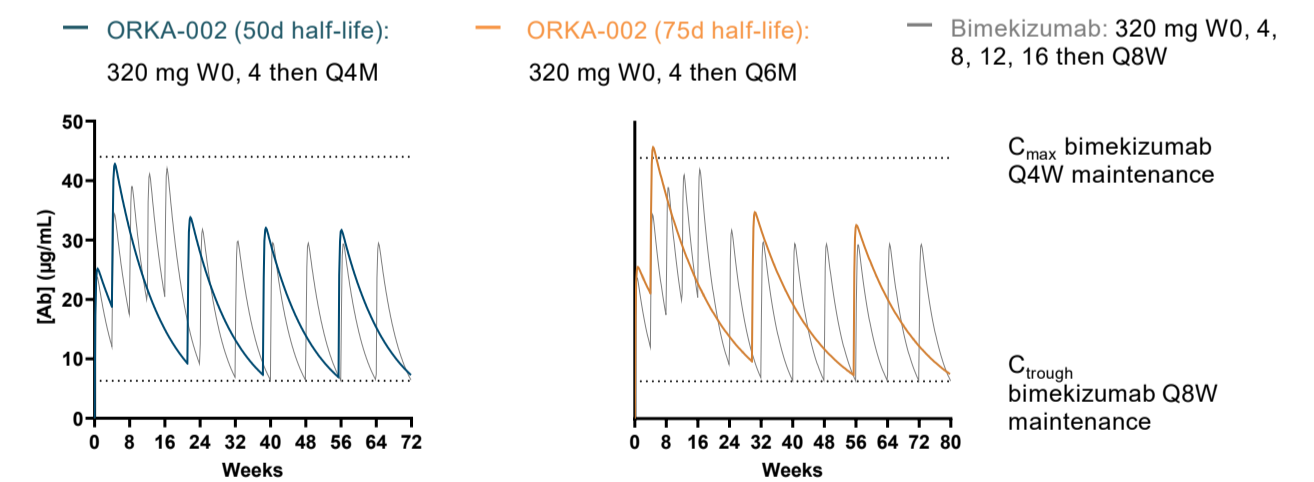


Notes: Study completed at Day 49

The half-life of ORKA-002 was significantly extended in cynomolgus monkeys compared to BIME (Figure 5). 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-002 SC group).

### Figure 6: Predictive simulations of ORKA-002 PK in humans support dosing every four to six months

#### Projected exposure of illustrative ORKA-002 regimens vs. approved bimekizumab regimens



- Predictive simulations of ORKA-002 PK in humans suggest that a half-life of ~50 days would enable subcutaneous maintenance dosing every 4 months and a half-life of ~75 days would enable dosing every 6 months while maintaining trough antibody concentrations equal to or above bimekizumab (Figure 6).
- YTE-modified antibodies on average have a human half-life that equals approximately 2-4x the NHP half-life. The half-life for ORKA-002 observed in NHPs therefore supports the potential to achieve at least Q4M and even Q6M dosing.

Notes: Bimekizumab modeling, Cmax, and Ctrough are based on published PK parameters from FDA and EMA review documents

## Conclusions

- ORKA-002 exhibits high affinity and selectivity for IL-17A and IL-17F and potent inhibition of downstream cellular signaling
- ORKA-002 demonstrated a half-life of ~25 days in cynomolgus monkeys, which exceeds that of bimekizumab by ~3-fold
- ORKA-002 has the potential to match bimekizumab on potency while requiring only two or three doses per year
- These data provide preclinical evidence of ORKA-002's clinical potential to meaningfully improve upon currently available therapies for psoriasis and psoriatic arthritis

For further information please contact MedAffairs@orukatx.com

