



ORUKA
THERAPEUTICS

Corporate Overview

NASDAQ: ORKA

September 2024

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On a mission to enable freedom from chronic skin disease

Our goal

Help patients with chronic skin conditions experience the **greatest possible freedom from disease**



Our approach

Advance potentially **best-in-class, half-life extended monoclonal antibodies** targeting mechanisms with **proven efficacy and safety**

PROGRAM	DISCOVERY	IND-ENABLING	CLINICAL	POTENTIAL INDICATIONS
ORKA-001	IL-23p19		FIH 1Q25 HV PK 2H25	Psoriasis
ORKA-002	IL-17A/F		FIH 3Q25	Psoriasis, psoriatic arthritis, others
ORKA-003	Undisclosed			

Rights to development candidates acquired from Paragon Therapeutics, the source of the technology behind Apogee and Spyre

Psoriasis is the ideal indication space for our strategy



Large, well-validated market with proven ability for differentiated new entrants to gain share



Best targets established with IL-23p19 and IL-17A/F – unlikely that new mechanisms can improve on the standard of care



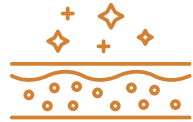
Physicians want new and better biologics – the field has focused on orals, but they have consistently fallen short of biologic efficacy



Extensive clinical precedent exists from prior programs to inform development of an optimal biologic

ORKA-001 and ORKA-002 complement each other

ORKA-001



For patients with purely skin disease



**Majority of dermatologists prefer
an anti-IL-23p19**

ORKA-002



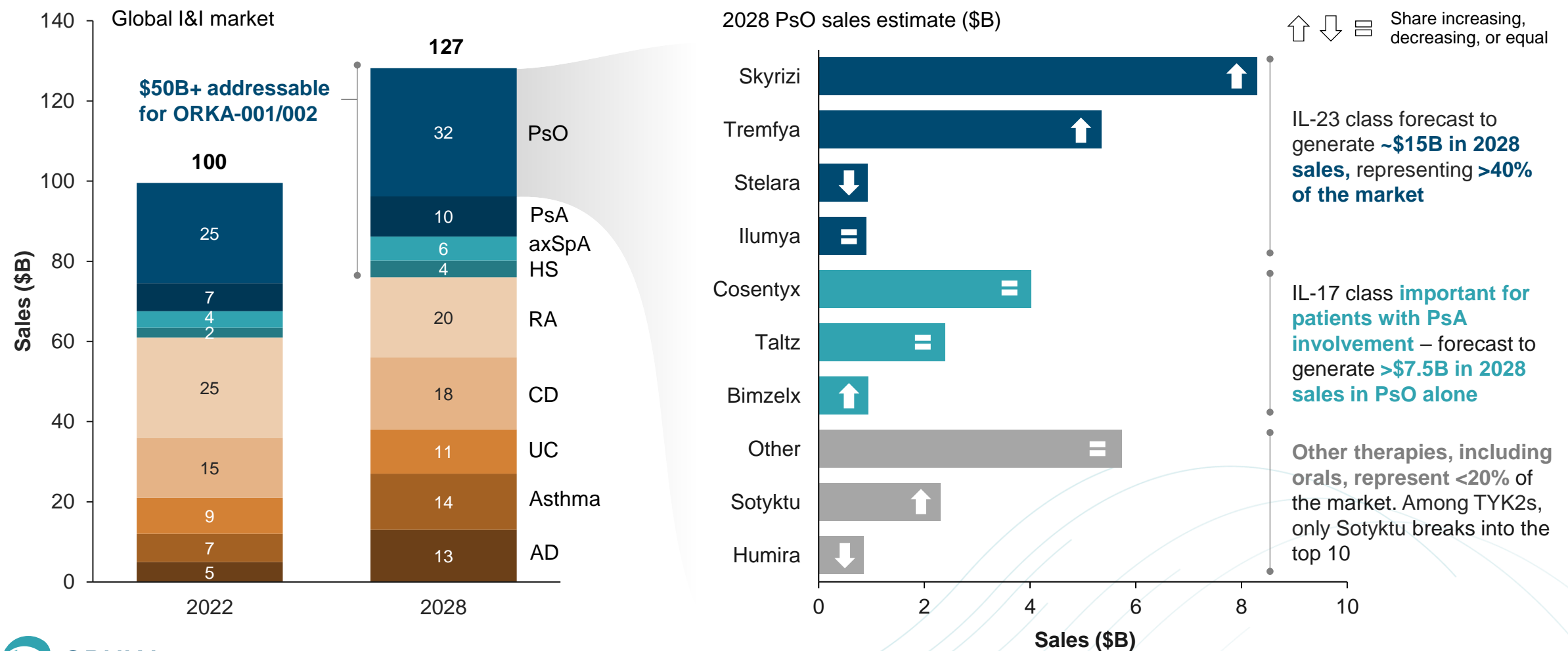
For patients with joint involvement, including
PsA, or recalcitrant skin disease

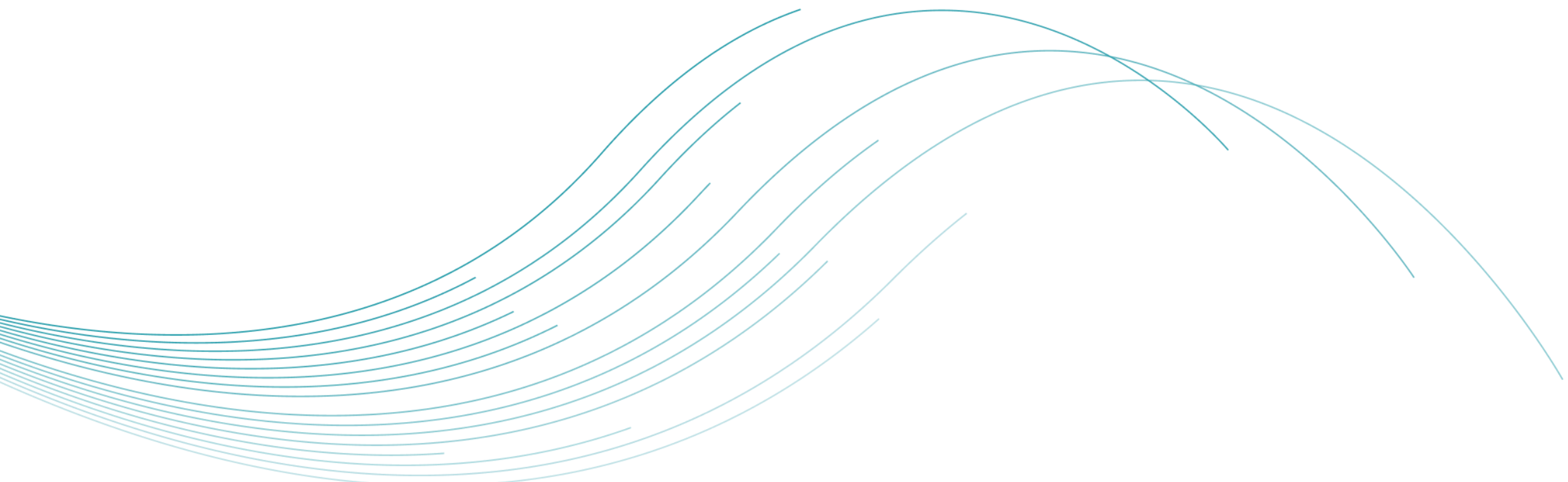


**Anti-IL-17 preferred, and IL-17A/F
emerging as the best approach**

Our programs target a \$50B+ total market opportunity

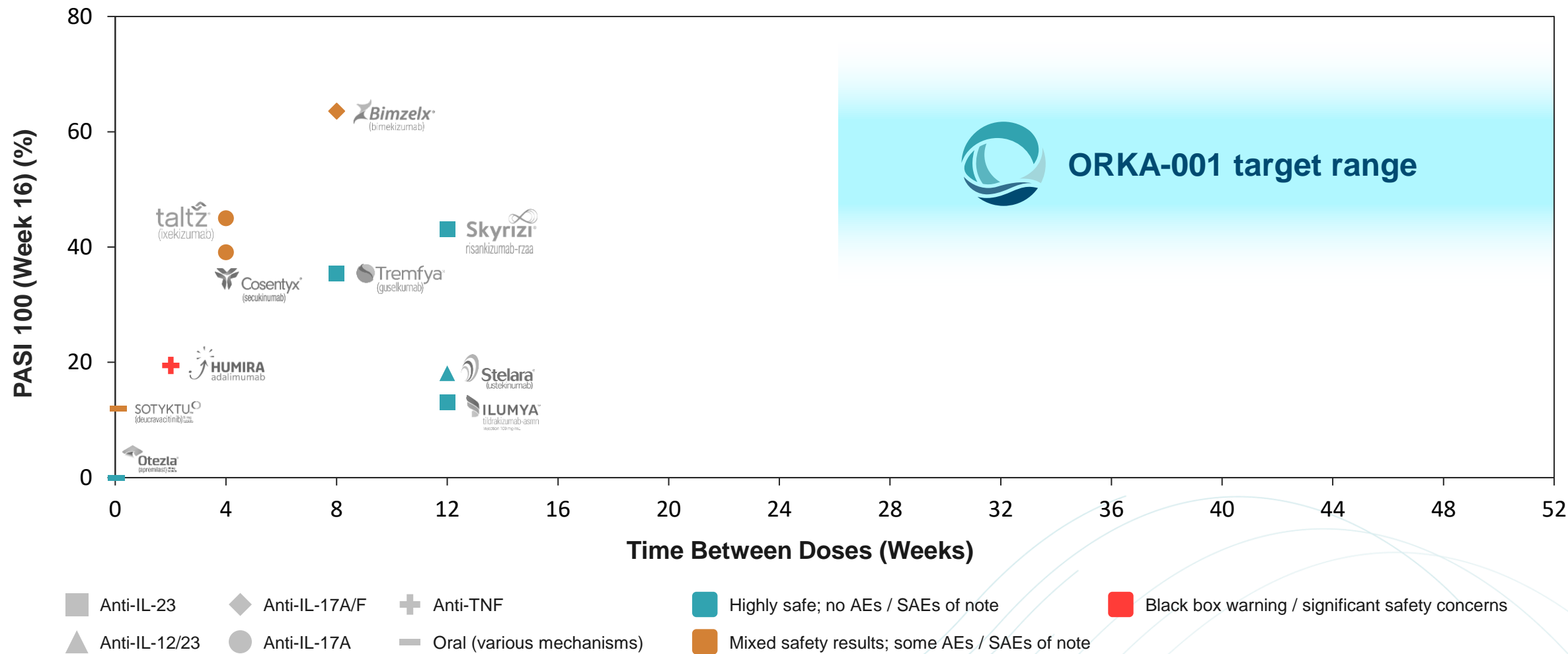
ORKA-001/002 target the dominant mechanisms in the largest I&I market



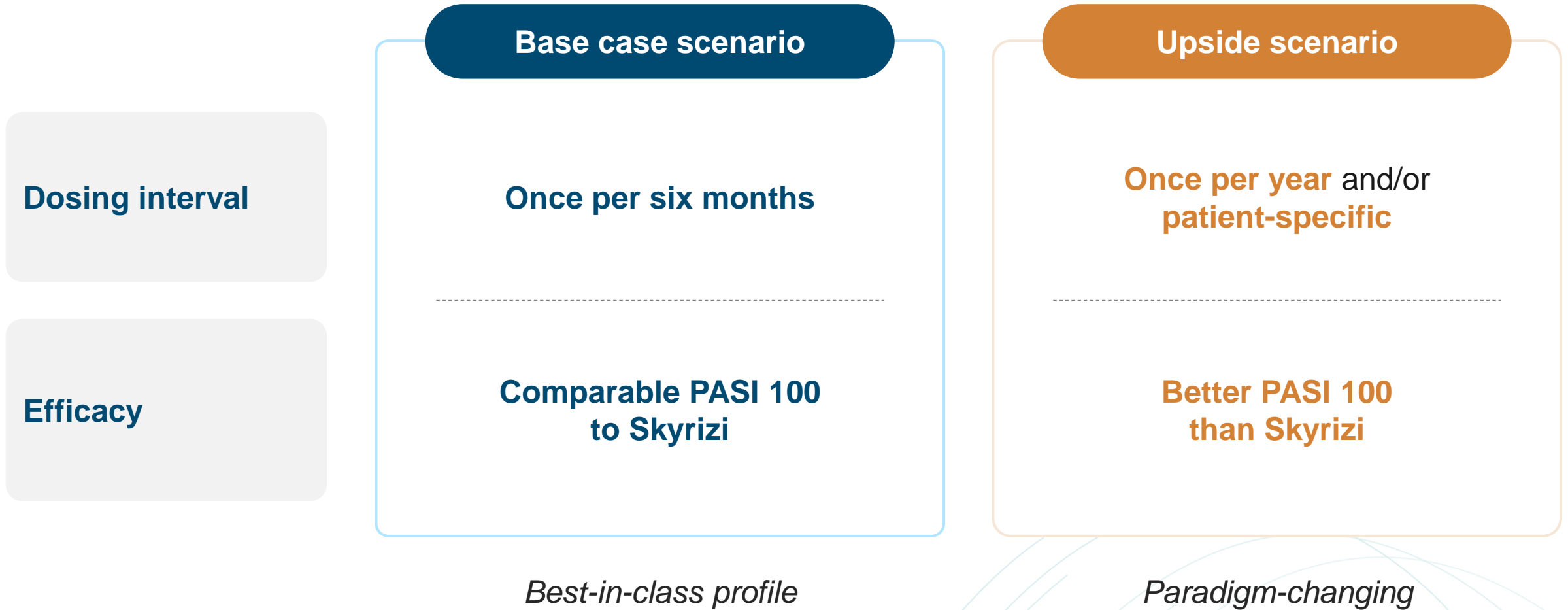


ORKA-001: potentially best-in-class anti-IL-23p19

Biologics have raised the bar on standard of care in PsO, but there is ample room for improvement



Base case is best-in-class, upside could be paradigm changing



ORKA-001 could be the last word in IL-23p19 inhibitors

Similar epitope to Skyrizi (risankizumab) with equal or better potency

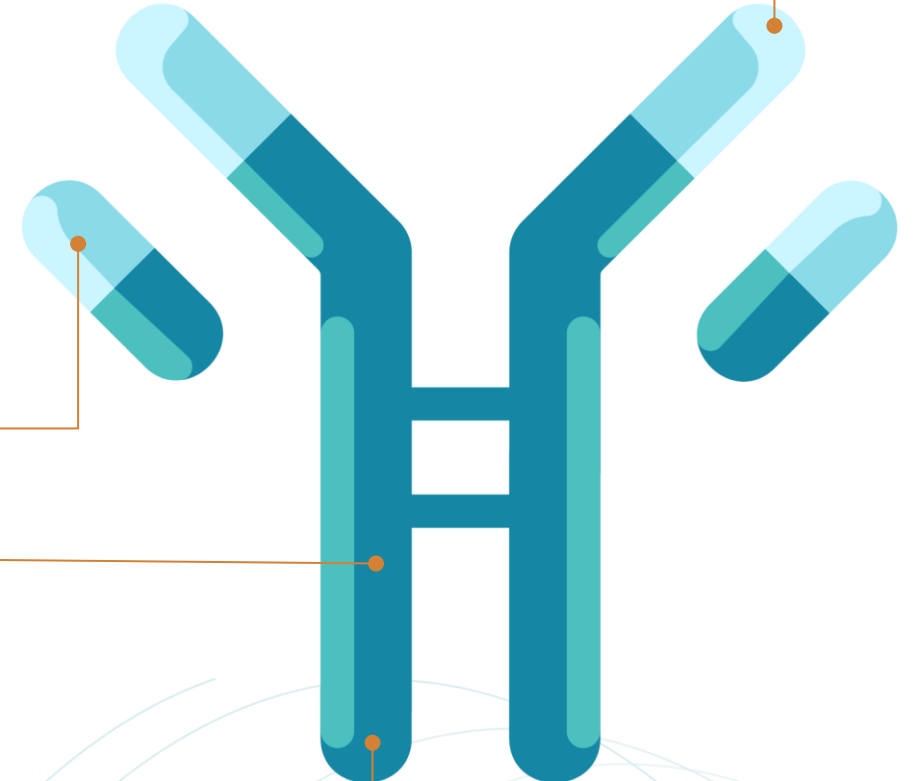
- Validated mechanism of action
- Binds **specifically to IL-23p19** (not IL-12/23 p40)
- **$K_D < 20$ pM**
- Predicted **equivalent safety**
- Predicted to **meet or beat efficacy**

Novel IP for composition of matter into 2040s

Half-life extension through validated Fc modification (YTE mutations)

- **Higher exposure** to increase efficacy
- **Longer exposure** to reduce dosing frequency

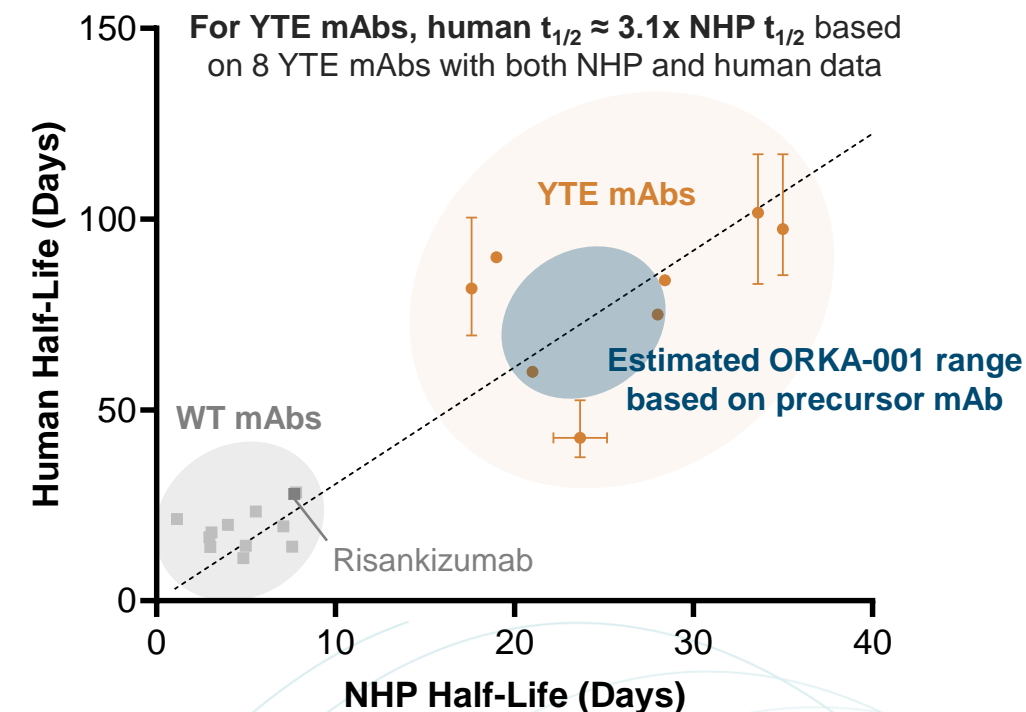
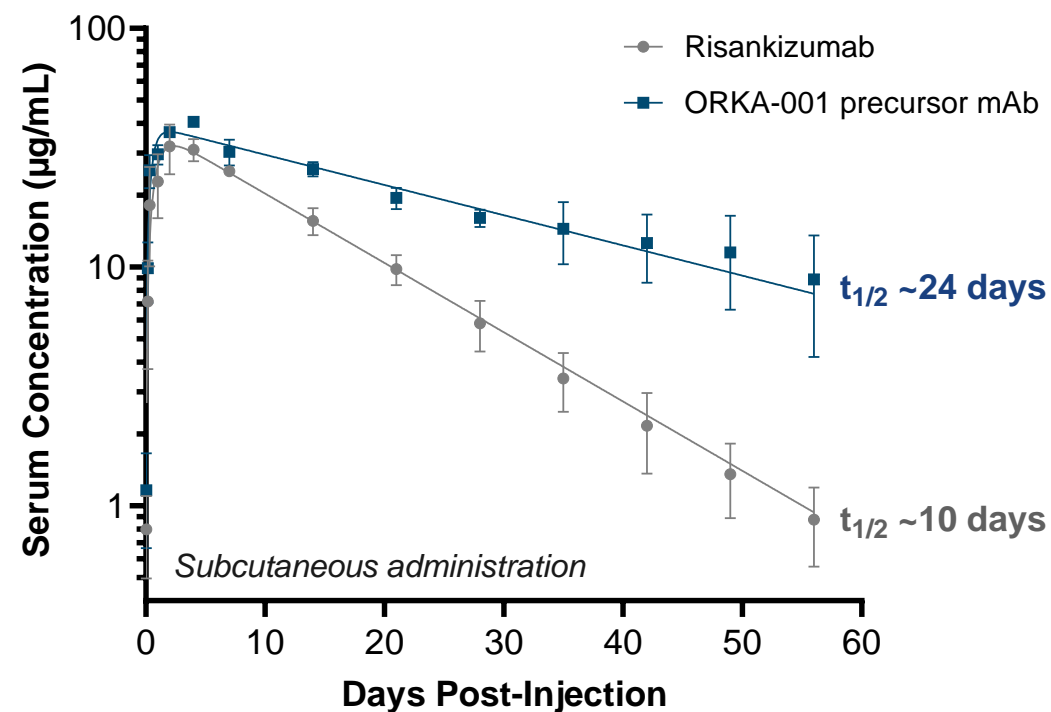
Effector-null human IgG1 Fc



Clinical experience with YTE predicts significant $t_{1/2}$ extension

2.4x longer half-life than Skyrizi with precursor mAb in NHPs

Implies ORKA-001 could have a significantly longer half-life in humans

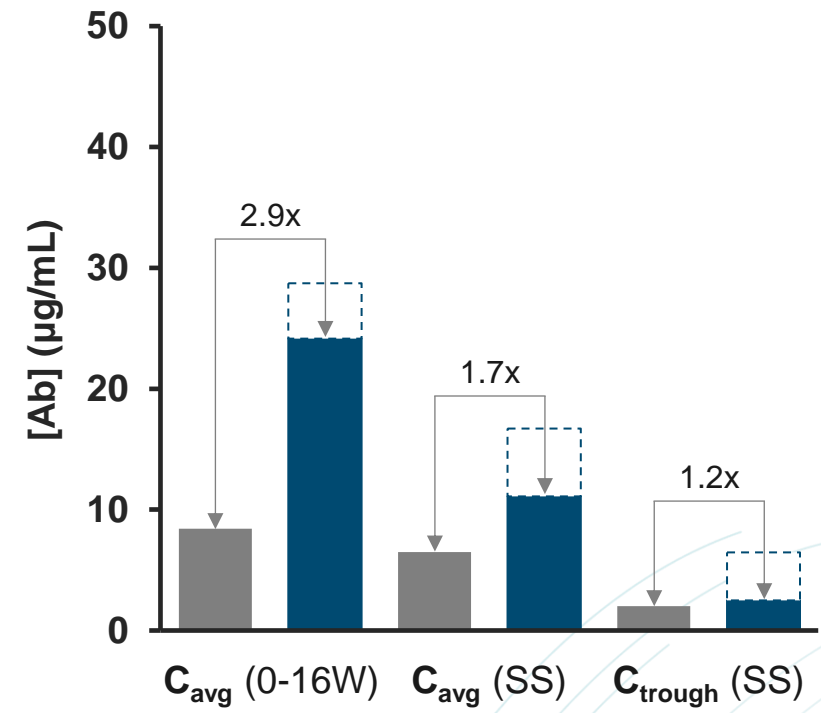
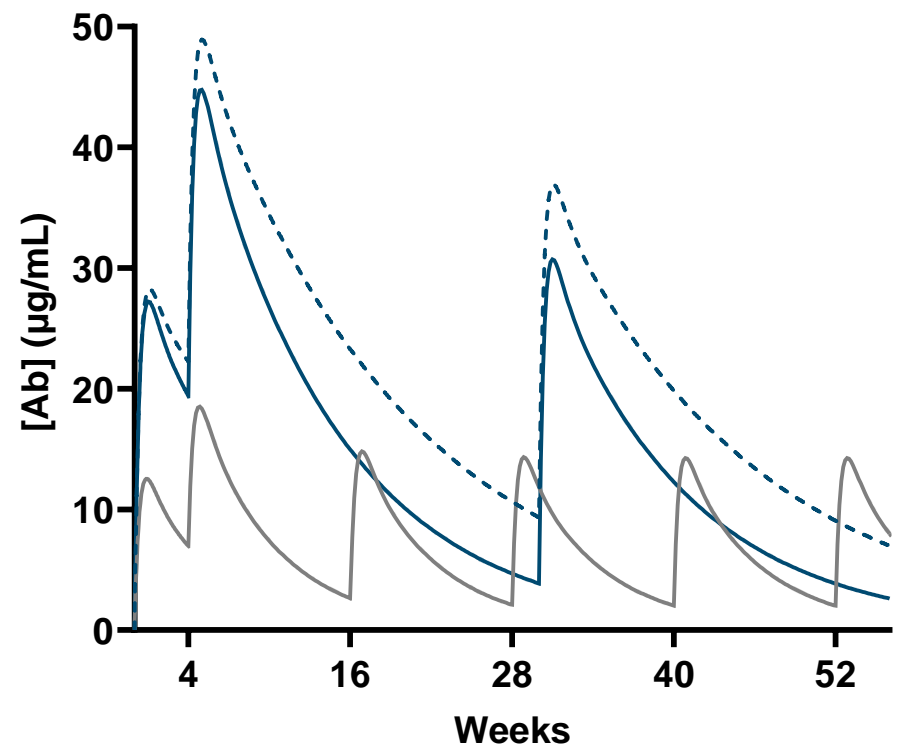


New data to be presented at EADV in September shows that **ORKA-001 has a half-life of >30 days in NHPs**

Base case is achievable even at lower end of predicted half-life

ORKA-001 exposure could exceed SKYRIZI under a variety of half-life scenarios

- ORKA-001 (50d half-life): 300 mg W0, 4, Q6M
- - - ORKA-001 (74d half-life): 300 mg W0, 4, Q6M
- Skyrizi: 150 mg W0, 4, Q12W (approved regimen)



Even at a 50-day half-life, Q6M dosing with ORKA-001 is projected to give a significantly higher C_{avg} and C_{trough} than Skyrizi

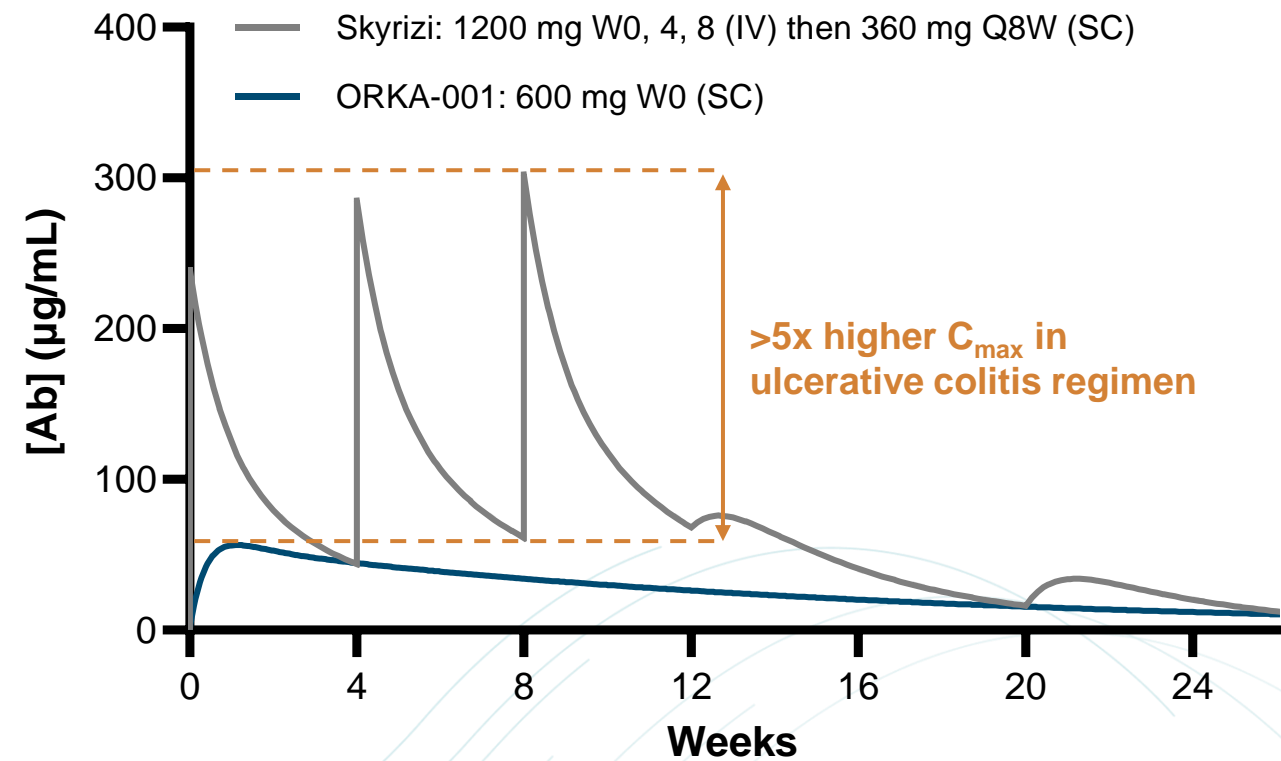
ORKA-001 benefits from a large body of clinical evidence with IL-23 inhibition

Very uncommon to have clinical precedent in large numbers of patients for the safety of higher exposures

- Peak and average exposures of ORKA-001 dosed at 600 mg are **multiples lower** than those with approved Skyrizi regimens in IBD
- No correlations observed at the patient level between exposure and safety signals **across >4,000 patients dosed** with Skyrizi in clinical trials

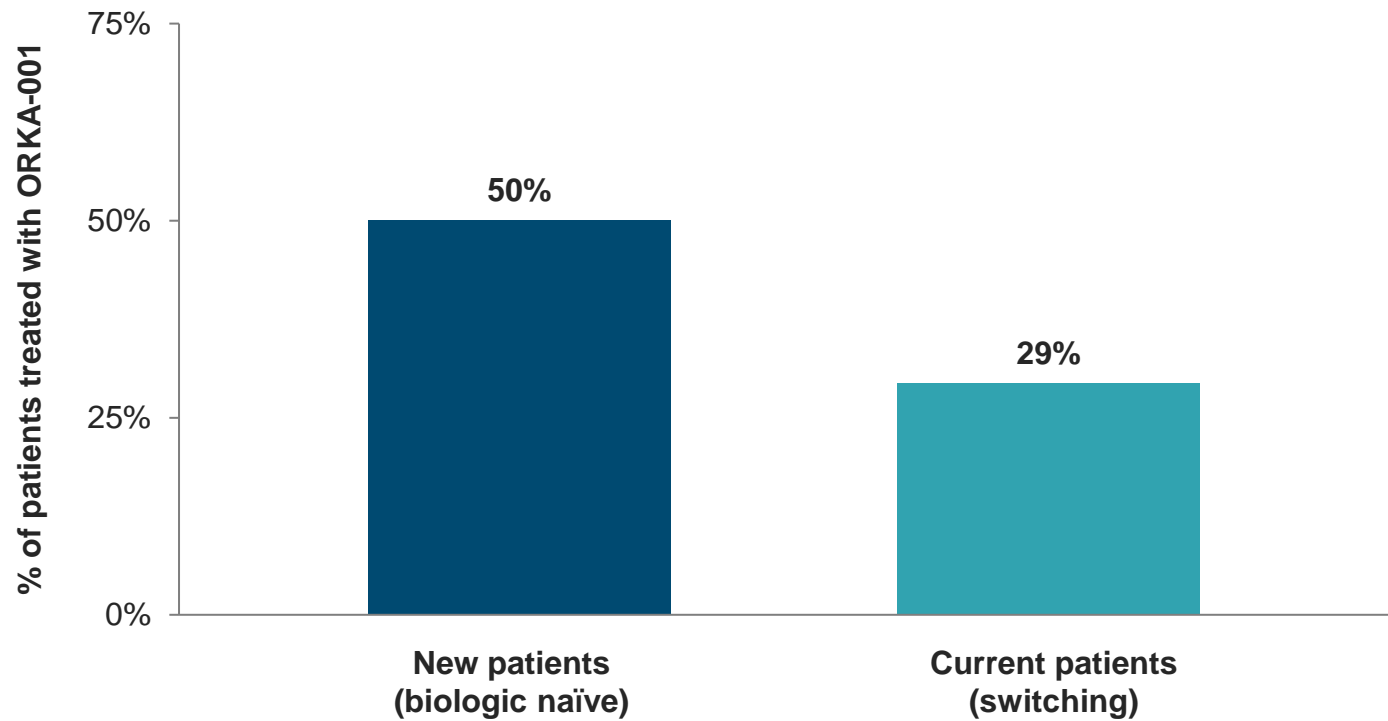
All five IL-23p19 inhibitors with published data in psoriasis have performed as expected based on their biophysical properties

Skyrizi regimen in UC establishes the safety of very high exposures









Dermatologists view the “base case” as highly attractive

In the “base case,” dermatologists would put half of new patients on ORKA-001 even when accounting for entry of new oral medicines



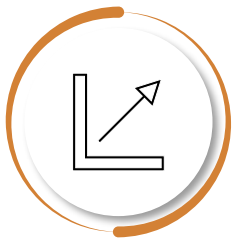
Multiple examples support dosing as a major commercial differentiator:

PsO	 risankizumab-rzaa Q12W	vs.	 (guselkumab) Q8W
Asthma	 (benralizumab) injection 30mg Q8W	vs.	 (mepolizumab) Q4W
wAMD	 (afibercept) Injection Q8W	vs.	 RANIBIZUMAB Q4W

Increasing excitement about drugs with long dosing intervals:

- Positive Phase 3 results for depemokimab (GSK), ocrelizumab (Roche), lenacapavir (Gilead), all given twice-yearly
- GSK acquired Aiolos for a long-acting YTE mAb targeting TSLP

Three potential upside scenarios for ORKA-001



Superior efficacy

Higher exposure could drive higher PASI 100



1-year dosing interval

Enabled by half-life extension



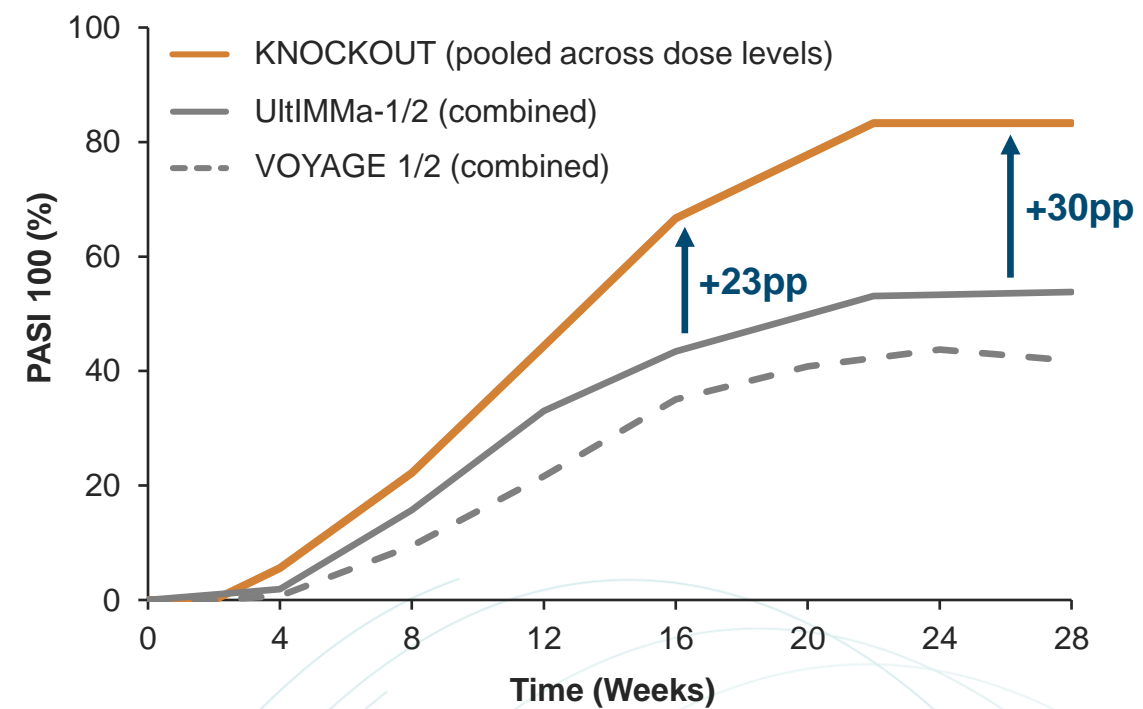
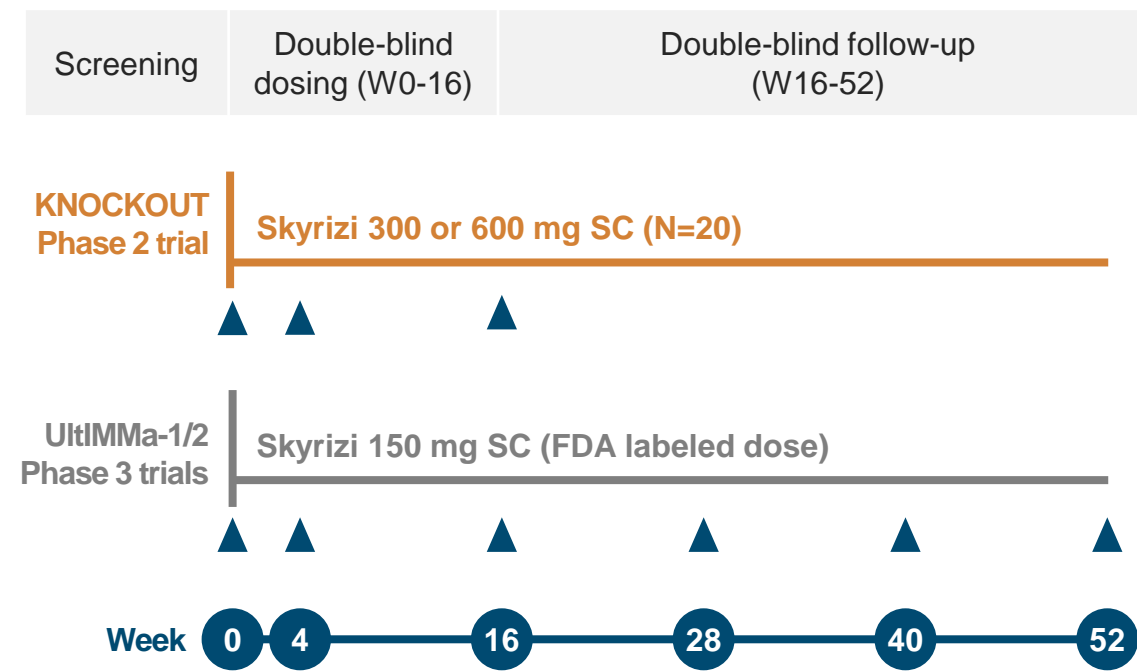
Disease modification

Patient-specific dosing to allow for treatment-free remissions

Higher exposures drove higher efficacy in KNOCKOUT study

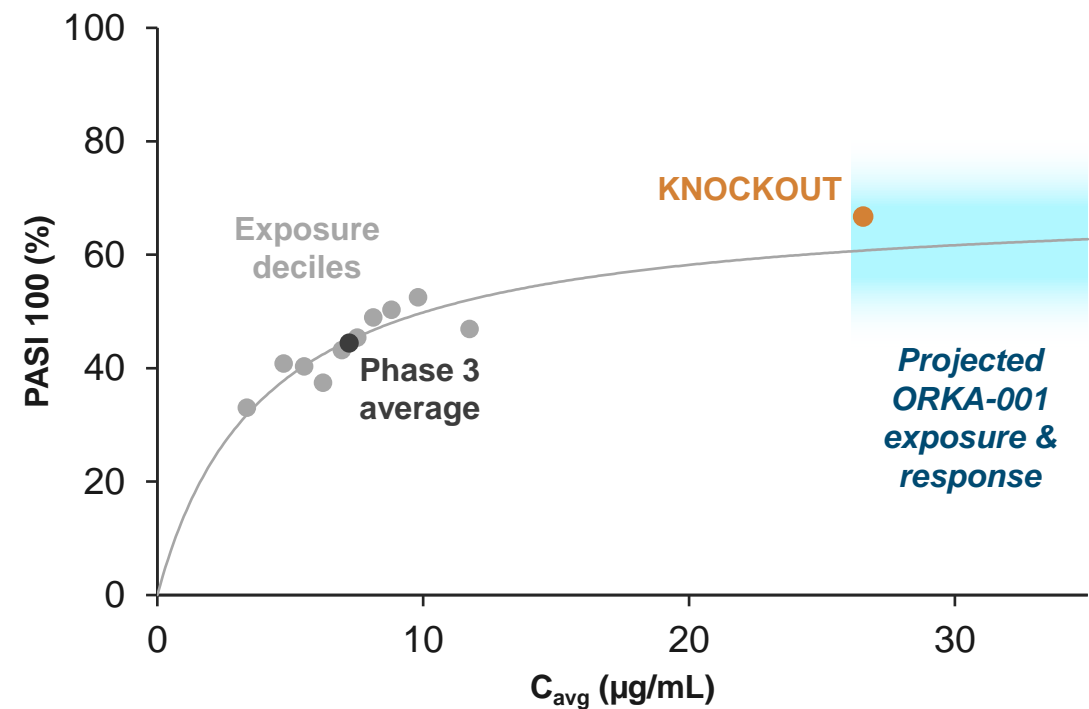
KNOCKOUT evaluated 2-4x the approved Skyrizi dose...

...and resulted in the highest PASI 100 rates observed to date

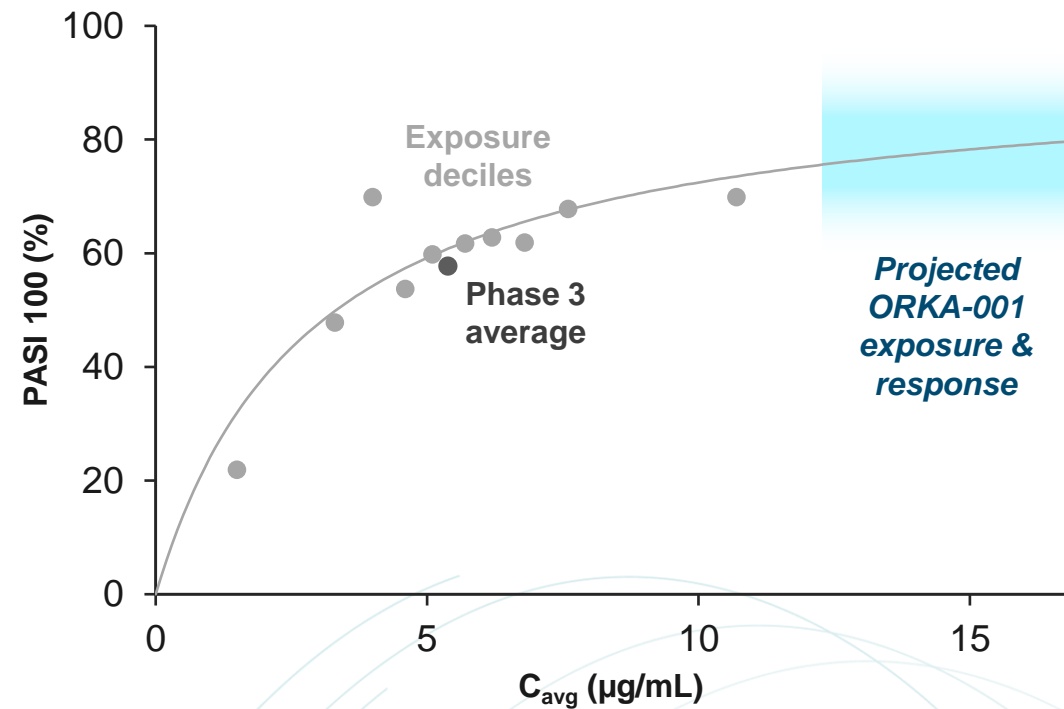


ORKA-001 could drive higher efficacy based on KNOCKOUT and a consistent exposure-response trend across trials

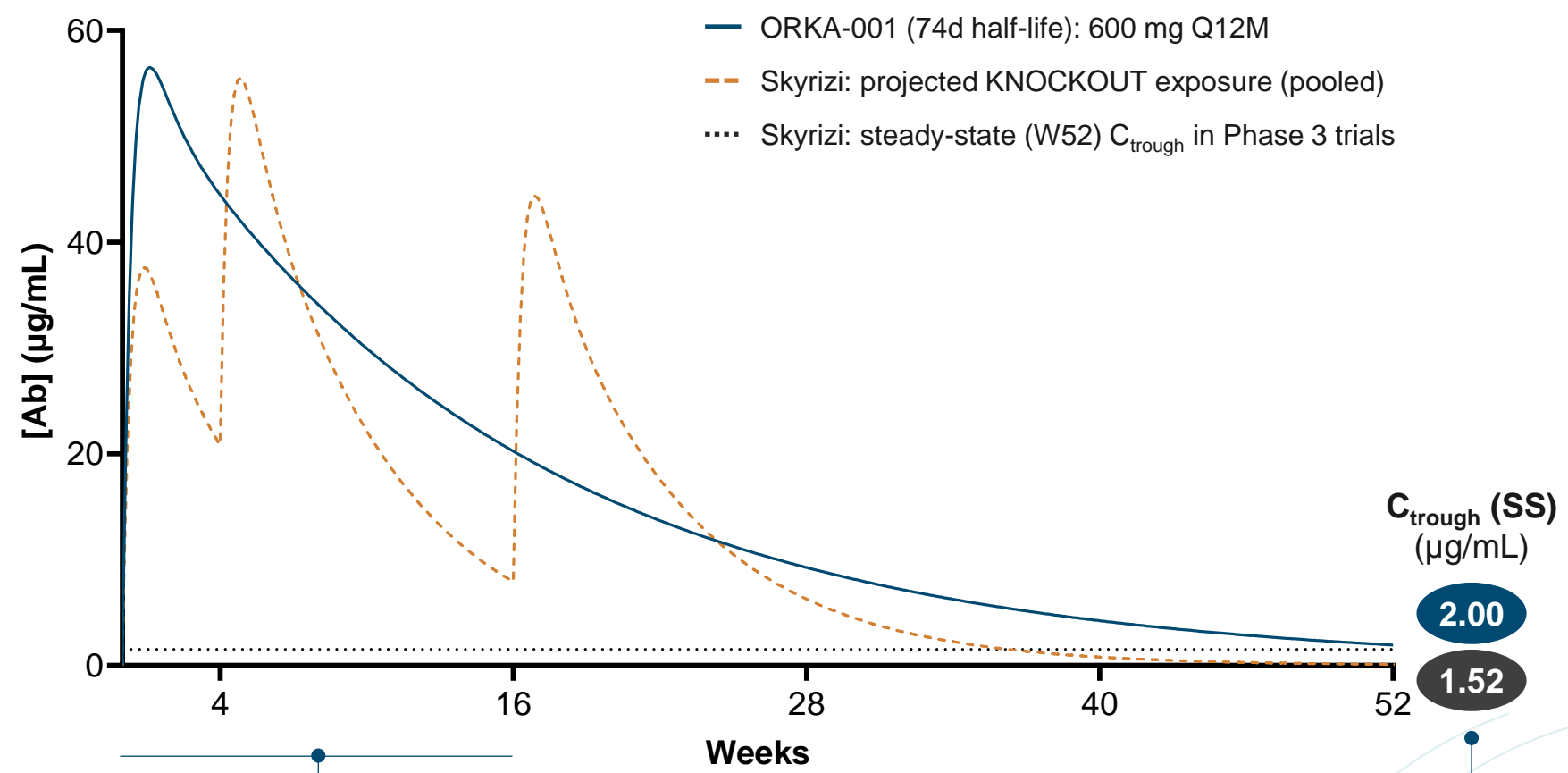
Induction phase (0-16 weeks)



Steady-state phase (40-52 weeks)



KNOCKOUT-like exposures are possible with one dose per year



With a 74-day half-life, ORKA-001 at one dose per year could match or exceed both KNOCKOUT early exposures and steady-state trough levels of standard Skyrizi dosing

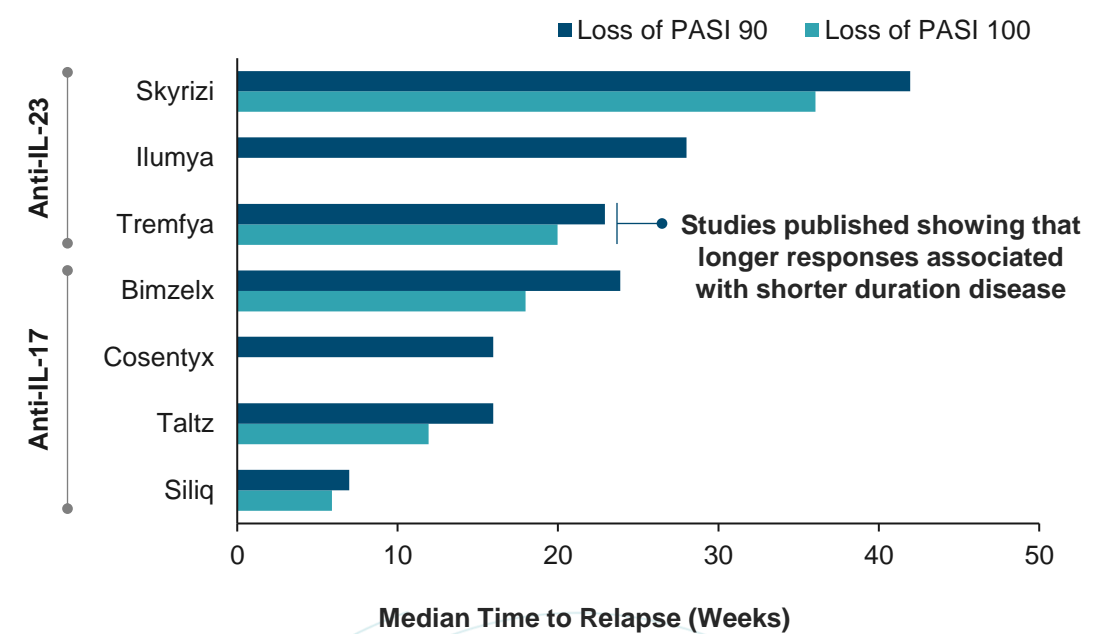
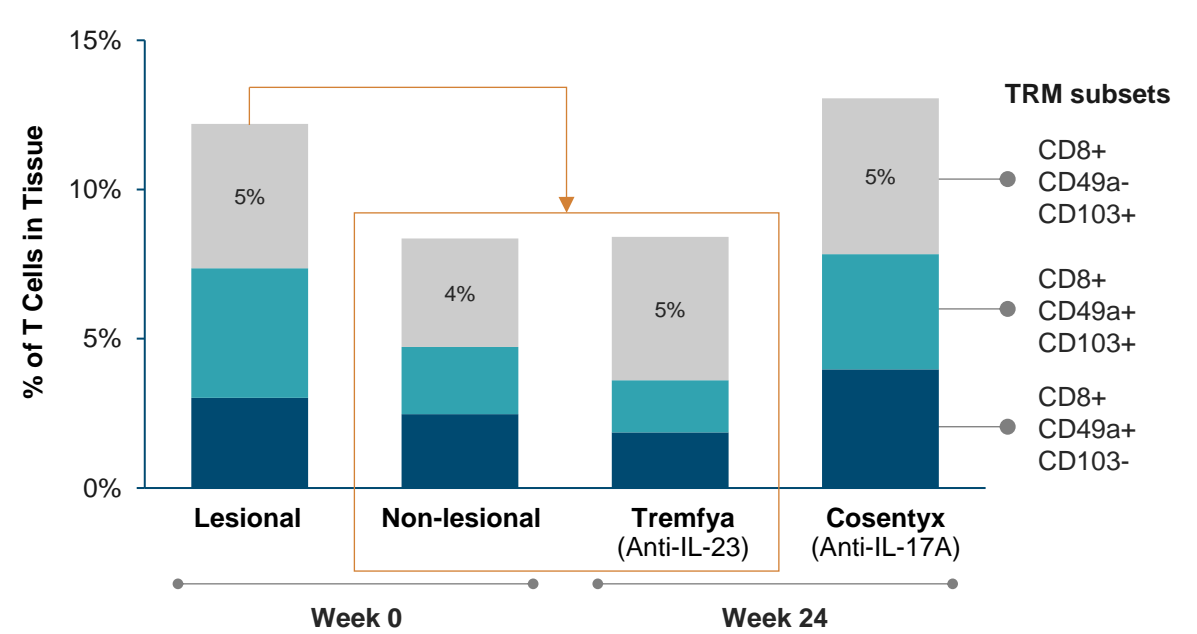
Comparable or greater early exposure vs. KNOCKOUT

Comparable or greater steady-state C_{trough} vs. Skyrizi

Potential for disease modification or cure by depleting TRMs

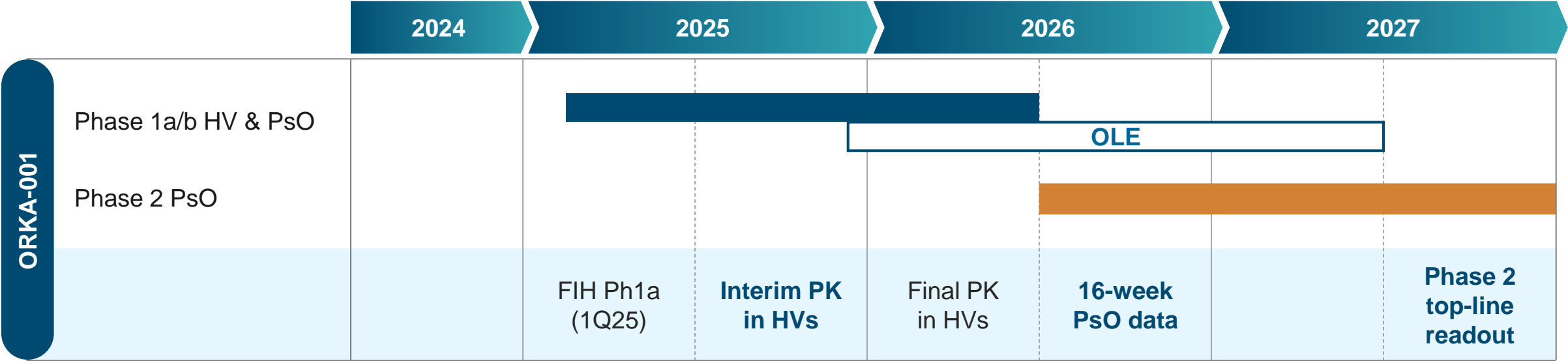
Anti-IL-23 acts upstream of disease-causing TRMs, and has a unique ability to deplete them from tissue

Leading to long-lasting remissions after treatment withdrawal – pointing to possibility of disease modification



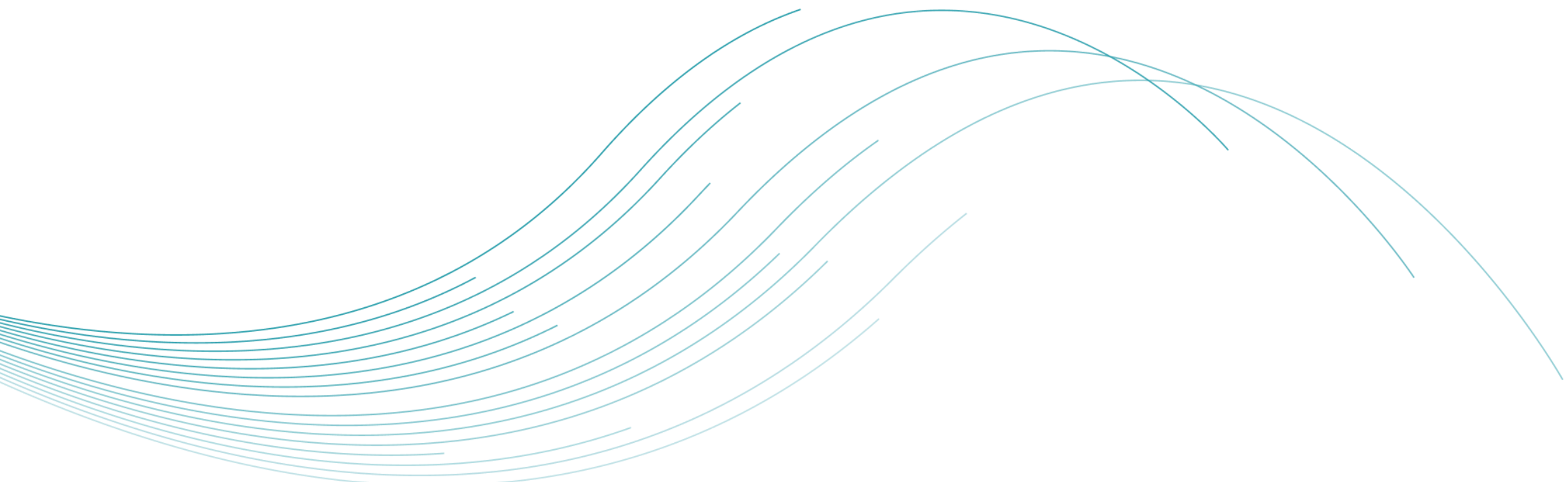
Excitement growing in dermatology community to **test disease modification potential of high anti-IL-23 exposures early in disease – a perfect opportunity for ORKA-001**

ORKA-001 development path sets up a catalyst-rich next 3 years



Potential for rapid de-risking, value recognition, and path to BLA

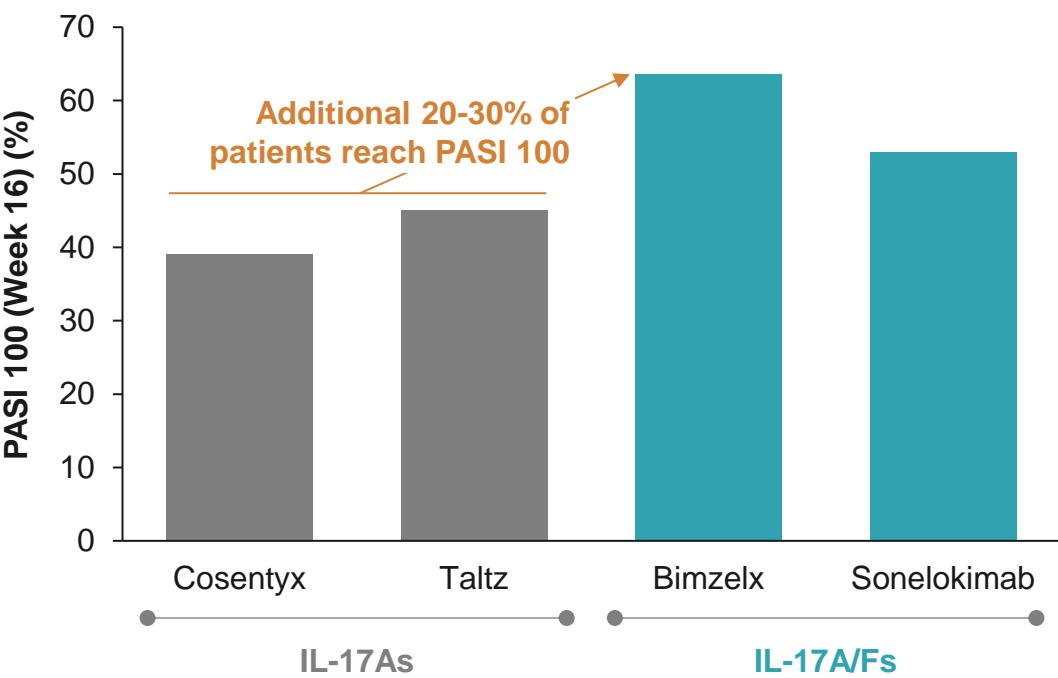
- **Interim PK data is highly validating**, showing both basis for differentiation and early safety
- Validated clinical endpoints (e.g., PASI 100) show **highly robust correlation between Phase 2 and 3**
- Rapid timelines possible in PsO – **average time from FIH to BLA/NDA is 6.5 years**



ORKA-002: potentially best-in-class anti-IL-17A/F

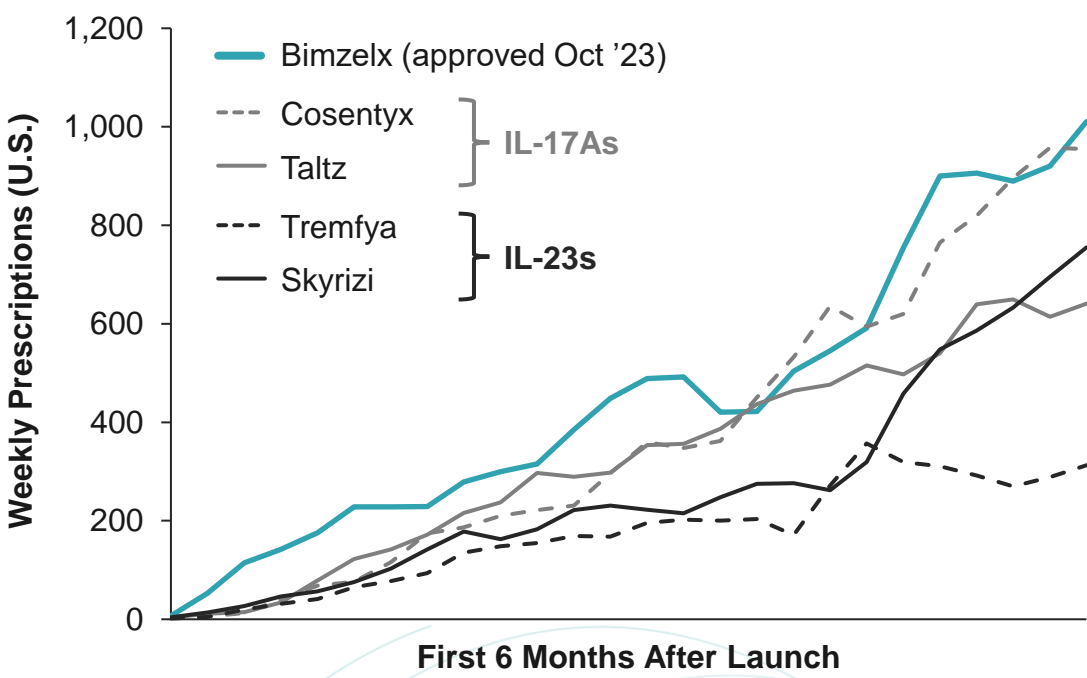
IL-17A/F dual blockade has emerged as the superior strategy

IL-17A/F shows superior efficacy to IL-17A in PsO









Superior efficacy in other indications as well

Bimzelx has had a very strong launch, validating both IL-17A/F and the ability to differentiate in PsO



Bimzelx consensus peak sales estimate of \$4.5B

The two leading IL-17A/Fs leave room for improvement

	 (bimekizumab-bkzx)	Sonelokimab <i>No further development planned in PsO</i>	ORKA-002 <i>Target product profile</i>
Format	Full-length, dual targeting mAb	Trivalent structure with nanobodies targeting IL-17A/F, IL-17F, and albumin	Full-length, dual targeting, half-life extended mAb
Doses per year (PsO maintenance)			
Clear dose response			Expected similar to Bimzelx
Minimal risk of neutralizing ADAs	~15-25% of patients had ADAs; no clinical impact	~30% of patients had ADAs in Phase 1; TBD in late-stage trials	Expected similar to Bimzelx

ORKA-002 could be the best-in-class IL-17A/F inhibitor

Similar epitope to Bimzelx (bimekizumab) with equal or better potency

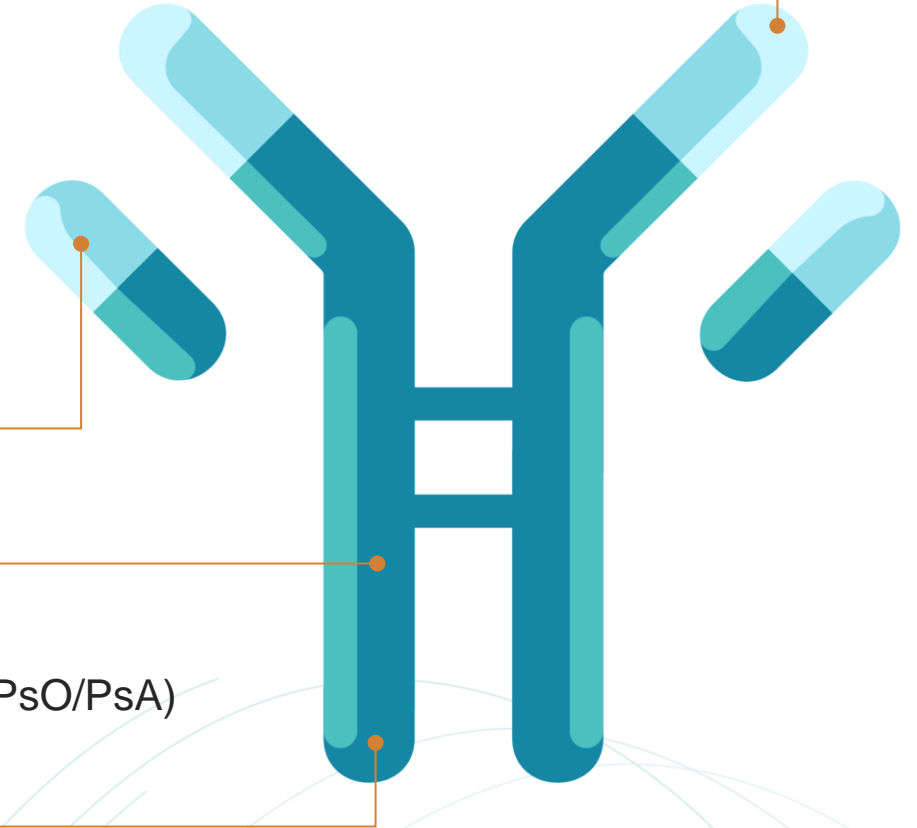
- Validated mechanism of action
- Binds **IL-17A and IL-17F** to prevent homodimer and heterodimer signaling
- **Equal or greater affinity** vs. bimekizumab
- Predicted **equivalent safety**
- Predicted to **meet or beat efficacy**

Novel IP for composition of matter into 2040s

Half-life extension through validated Fc modification

- **Higher exposure** to increase efficacy
- **Longer exposure** to reduce dosing frequency (targeting 2-3 doses/year in PsO/PsA)

Effector-null human IgG1 Fc



ORKA-002 could be best-in-class in a \$15B market



Best target

- Dual IL-17A/F inhibition has shown superior efficacy vs. IL-17A
- **\$15B+ in future market potential**



Best profile

- Skyrizi-like dosing intervals or longer
- Reduced biological risk by pursuing Bimzelx MoA



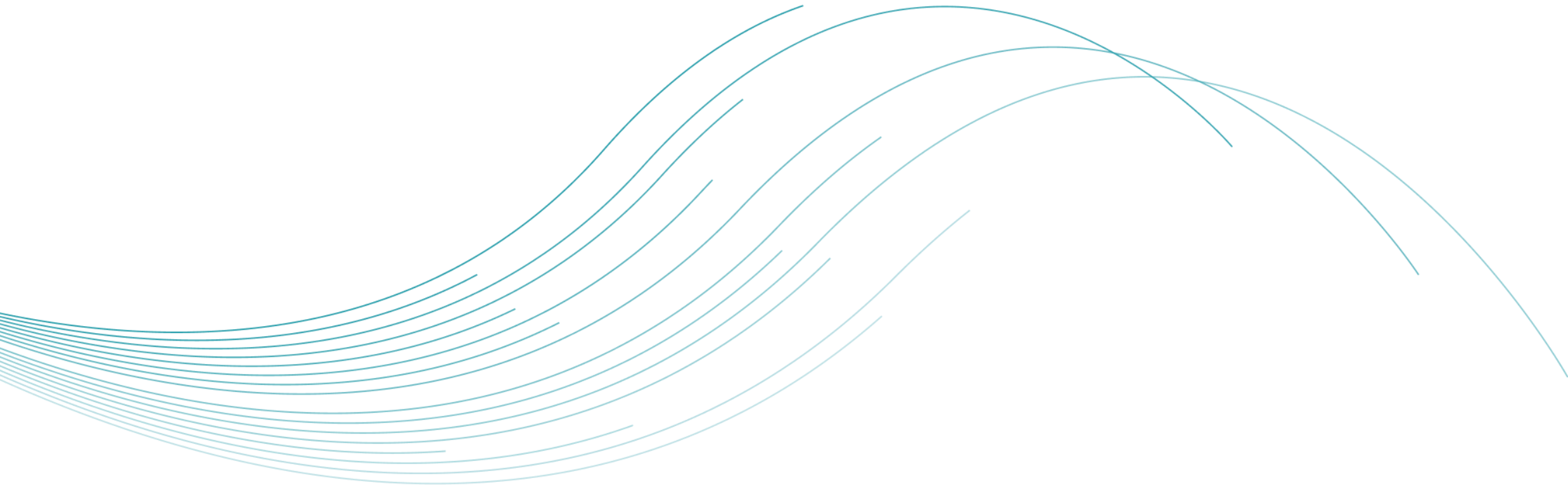
Limited competition

- Few other IL-17A/F inhibitors in development
- Lengthy timeline to biosimilar entry



Rapid development path

- Ph1 HV study de-risks PK and dosing interval
- Potential for **rapid development path** – Bimzelx took ~6 years from IND to BLA



Corporate

Multiple inflection points across the pipeline over the next 2+ years

	2024	2025		2026	
ORKA-001		FIH Ph1a (1Q25)	Interim PK in HVs	Final PK in HVs	16-week PsO data
ORKA-002			FIH Ph1 (3Q25)	Interim PK in HVs	
ORKA-003		Target disclosure			

Building rapidly with backing from Paragon



Lawrence Klein
CEO



Joana Goncalves
CMO



Paul Quinlan
General Counsel



Laura Sandler
SVP, Operations



Arjun Agarwal
SVP, Finance



Christopher Finch
VP, Corp Dev & Strategy



Alan Lada
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VP, Head of CMC



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Peter Harwin
Managing Member,
Fairmount



Cameron Turtle
CEO, Spyre
Therapeutics



Lawrence Klein
CEO, Oruka
Therapeutics



Capitalization following close of merger with ARCA and financings

As of September 12, 2024		Number of shares ¹
Common stock	• Shares outstanding	35.0M
	• Preferred stock (as-converted to common stock)	13.9M
Common stock equivalents	• Pre-funded warrants	6.2M
Common stock and common stock equivalents		• Total outstanding² 55.1M

