Model-Based PsO–PsA Bridging for Phase 2 Dose Selection: A Case Study of the IL-17 Small Molecule Inhibitor JNJ-81241459

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Key Takeaways

- **Validated QSP and MBMA models link HV data to projected PsA efficacy through PsO responses.**
- **Model projections support evaluating a broad dose range in Phase 2 to characterize dose response and target placebo-adjusted ACR50 above a specified threshold.**
- **This workflow could support PsO–PsA bridging for other investigational PsA therapies.**

Background

IL-17 is a validated therapeutic target for the treatment of autoimmune diseases. Anti-IL-17 antibodies have demonstrated efficacy and received approval for psoriatic arthritis (PsA), psoriasis (PsO), ankylosing spondylitis (AS) and hidradenitis suppurativa (HS).

JNJ-81241459 is an investigational oral small molecule that selectively binds IL-17 to inhibit IL-17 receptor signaling and reduce tissue inflammation. A first-in-human trial in healthy volunteers (HV) provided pharmacokinetic (PK) and IL-17 target engagement (TE) data.

Quantitative systems pharmacology (QSP) modeling links target engagement to molecular and cellular networks to predict treatment effects on clinical endpoints.

Model-based meta-analysis (MBMA) integrates longitudinal clinical trial data to estimate treatment effects across trials and indications, and between-study variability.

We combined QSP and MBMA approaches to bridge PsO to PsA and inform PsA Phase 2 dose selection for JNJ-81241459.

Objectives

1. **Characterize JNJ-81241459 PK and TE in HV and predict PASI responses in PsO using the PsO QSP model.**
2. **Apply MBMA to bridge QSP-projected PASI responses to ACR50 outcomes in PsA and inform Phase 2 dose selection**

Methods

1. Target engagement

1. Fitted a target-binding model to first-in-human serum IL-17 biomarker data.
2. Applied PsO-specific parameters to the HV model to project skin IL-17 TE.

2. PsO QSP model

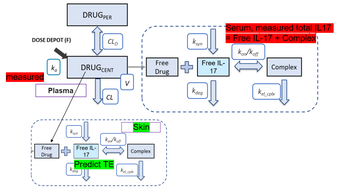
1. Built an ordinary differential equation (ODE) QSP network from literature and experimental data.
2. Calibrated and validated virtual patients using anti-IL-17, anti-IL-23 and JAK/TYK2 trial data.
3. Used skin TE to project PASI responses.

3. Joint MBMA model

1. Developed a longitudinal joint MBMA model using 4 approved IL-17 mAbs trial data, linking observed PsO PASI75 to PsA ACR50.
2. Applied QSP-projected PASI75 to this link, assuming biologic-like behavior.

Results

Target Engagement in HV and PsO

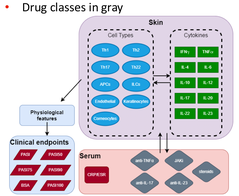


- We fitted the PK/TE model to measured serum drug concentrations and total IL-17 data to estimate drug PK and binding kinetic parameters (red). All other parameters retained their HV values.
- We adjusted the model for skin distribution and IL-17 turnover in PsO skin to simulate mean IL-17 TE over a dosing interval. The table summarizes dose-specific estimates and 90% confidence intervals (CIs).

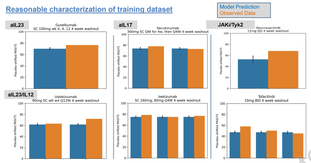
Dose	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
Mean %TE*	85.3 (69.6-92.0)	92.3 (81.5-95.7)	95.9 (90.1-97.8)	97.1 (92.4-98.4)	98.2 (95.1-99.1)

PsO QSP Model Development, Validation and PASI Projections for JNJ-81241459

PsO QSP model
- Cell types in blue, cytokines in green
- Clinical endpoints in red
- Drug classes in gray



- Week 12 placebo-adjusted PASI75 responses illustrate model performance (mean and 90% CI).



MoA	Drug	Trial	Training	Validation
aIL17	Ixekizumab	Gordon 2015 UNCOVER-1 Griffiths 2015 UNCOVER-2 Griffiths 2015 UNCOVER-3	**160mg: 80mg Q4W** **160mg: 80mg Q4W** **160mg: 80mg Q4W**	160mg: 80mg Q2W 160mg: 80mg Q2W 160mg: 80mg Q2W
	Secukinumab	Langley 2014 (ERASURE) Langley 2014 (FIXTURE)	**300mg SC Q4W** **300mg SC Q4W**	150mg SC Q4W 150mg SC Q4W
aIL12/23	Ustekinumab	Leonardi 2008 (PHOENIX 1) Papp 2008 (PHOENIX 2) Gordon 2018 (UIMMA-1) Gordon 2018 (UIMMA-2)	**90mg SC** **90mg SC** **45mg or 90mg SC** **45mg or 90mg SC**	45mg SC 45mg SC
Jak Inh	Tofacitinib	Papp 2015 (OPT Pivotal1) Papp 2015 (OPT Pivotal2) Bachelez, 2015 (OPT COMPARE) Papp 2012	**10mg BID** **10mg BID** **10mg BID** **2mg BID, 15mg BID**	5mg BID 5mg BID 5mg BID 5mg BID
aIL23	Guselkumab	Blauvelt 2017 (VOYAGE 1) Reich 2017 (VOYAGE 2) Reich 2019 (ECLIPSE) *	**100mg** **100mg** **100mg**	
	Risankizumab	Gordon 2018 (UIMMA-1) Gordon 2018 (UIMMA-2)		150mg 150mg
Tyk2 inh	Deucravacitinib	Papp 2018 Poster/Abstract (POETYK PSO-1/2) Press release (POETYK PSO-1/2)	**3mg Q2D, 3mg QD, 6mg BID,** **12mg QD**	3mg BID 6mg QD 6mg QD

- Included pivotal Phase 3 and informative Phase 2 trials with similar eligibility criteria.
- Fitted selected drugs and doses, then extrapolated to other drugs or regimens.
- Calibrated placebo effects using data from all included placebo groups.
- The PsO QSP model used projected skin TE as input.
- The model projected placebo-adjusted PASI75 and PASI90 responses at Weeks 12 and 16.
- **JNJ-81241459 doses ≥ Dose 4 yielded projected PASI responses similar to biologics**

Week 12		
Dose	PASI75	PASI90
Dose 1	38.8 (32.0-45.9)	27.3 (21.3-34.4)
Dose 2	51.5 (44.3-58.2)	35.7 (28.7-43.4)
Dose 3	58.8 (51.6-66.4)	43.9 (36.9-51.6)
Dose 4	71.7 (64.8-77.9)	43.9 (36.9-51.6)
Dose 5	73.8 (67.2-80.3)	61.4 (54.1-68.9)

Week 16		
Dose	PASI75	PASI90
Dose 1	42.3 (35.2-50.0)	34.6 (27.9-41.8)
Dose 2	51.5 (43.4-59.0)	41.2 (34.4-49.2)
Dose 3	71.9 (64.8-78.7)	49.3 (41.8-56.5)
Dose 4	76.1 (69.7-82.0)	63.6 (55.7-71.3)
Dose 5	76.1 (69.7-82.0)	63.6 (56.6-70.5)

MBMA Projections of JNJ-81241459 ΔACR50 in PsA

- The joint MBMA model was built from 51 studies with data up to 48 weeks: 4 treatments from the IL-17 drug class plus placebo, 129 trial arms, and 25,653 participants.
- QSP-projected PASI75 for JNJ-81241459 was applied to the MBMA-derived PASI75–ACR50 relationship, assuming biologic-like behavior, to project ΔACR50 in PsA.
- Projected ΔACR50 increased with dose and plateaued at ≥Dose 4.
- At Week 12, ΔACR50 ranged from 11.86% (Dose 1) to 24.02% (Dose 5); Dose 4 reached 22.94% (95% CI 15.4–31.9).
- Longitudinal projections increased from Week 12 to Week 16, with Dose 4 reaching 26.87% (95% CI 18.5–36.3).

Tables show projected ΔACR50 by dose at Weeks 12 and 16, where ΔACR50 is the placebo-adjusted ACR50 response (JNJ-81241459 minus placebo, percentage), as mean (95% CI)

Week 12	
Dose	ΔACR50 % (95% CI)
Dose 1	11.86 (6.6-18.9)
Dose 2	15.41 (9.2-23.2)
Dose 3	17.71 (11.1-26)
Dose 4	22.94 (15.4-31.9)
Dose 5	24.02 (16.3-33.1)

Week 16	
Dose	ΔACR50 % (95% CI)
Dose 1	13.58 (7.7-21.2)
Dose 2	16.36 (9.8-24.6)
Dose 3	24.43 (16.5-33.7)
Dose 4	26.87 (18.5-36.3)
Dose 5	26.87 (18.5-36.3)

Conclusions and interpretation

- We combined validated PsO QSP and MBMA models to project placebo-adjusted ACR50 with JNJ-81241459 at Weeks 12 and 16 in PsA.
- The QSP model projected PASI responses similar to biologics in PsO. We used the MBMA-derived PsO–PsA relationship to project corresponding ACR50 responses in PsA.
- These projections support evaluating a broad dose range in Phase 2 to characterize dose response and maximize the likelihood of achieving a specified placebo-adjusted ACR50 threshold in a mixed PsA population.
- The framework links HV data to projected patient outcomes and uses PsO–PsA bridging to inform dose selection.
- This workflow could support disease bridging for other immunology therapies, subject to model adaptation and validation.
- These model projections assume biologic-like behavior for JNJ-81241459 in the MBMA and require clinical confirmation.

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