Exposure-Response Relationship of Icotrokinra Effects in Participants With Moderate-to-Severe Plaque Psoriasis: Phase 2b FRONTIER 1&2 Results

Emily Bozenhardt,[1] Yu Kyoung Cho,[1] Yuan Xiong,[1] Wangda Zhou,[1] Brinda Tammara,[1] Cynthia DeKlotz,[1] M. Claire Holland,[1] Ya-Wen Yang,[1] An Vermeulen,[1] Mahesh N. Samtani[1]
[1]Johnson & Johnson, Spring House, PA, USA

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Introduction

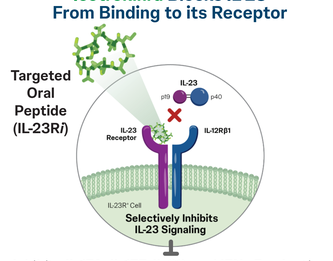
Icotrokinra (ICO)

- Targeted oral peptide that selectively blocks the interleukin (IL)-23 receptor and inhibits IL-23 pathway signaling[1]
- ICO showed greater clinical response rates than placebo (PBO) in participants with moderate-to-severe plaque psoriasis (PsO) in the Phase 2b FRONTIER 1 study, with response rates durable through 1 year of the FRONTIER 2 long-term extension (LTE) study[2,3]

Objectives

Characterized the relationships between ICO systemic exposure and clinical response in the Phase 2b FRONTIER 1 & 2 studies that informed dose selection for Phase 3

Icotrokinra Blocks IL-23 From Binding to its Receptor



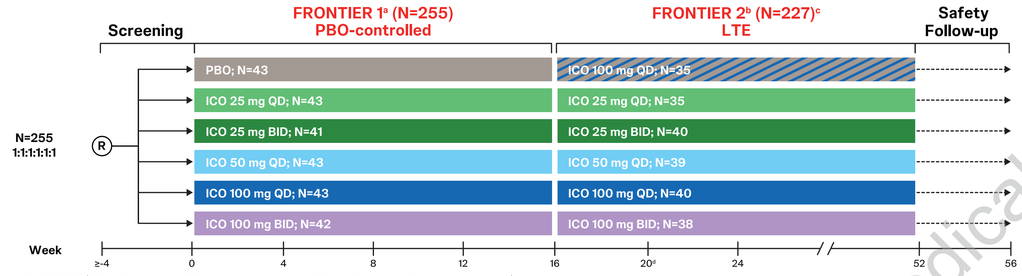
Inhibits IL-17A, IL-17F, IL-22, and IFNγ Production

*IFN=interferon; **IL-23Ri**=interleukin-23 receptor inhibitor.*

FRONTIER 1 & FRONTIER 2 Study Designs

Key inclusion criteria:

- Moderate-to-severe plaque PsO
  - ≥18-years-old
  - PASI ≥12
  - IGA ≥3
  - BSA ≥10%
- Diagnosed with PsO, with or without psoriatic arthritis, for ≥6 months
- Candidate for phototherapy or systemic therapy



[a]NCT05223868. [b]NCT05364554. [c]At W16, 227 participants from FRONTIER 1 entered FRONTIER 2 LTE study. [d]Final safety follow-up for participants who did not enter the LTE. Those not participating in the LTE completed 4 weeks of safety follow-up to complete the FRONTIER 1 study. ***BID***=twice daily; ***BSA***=body surface area; ***IGA***=Investigator's Global Assessment; ***PASI***=Psoriasis Area and Severity Index; ***QD***=once daily; ***R***=randomization; ***W***=week.

Key Takeaways

Findings from the Phase 2b FRONTIER 1 & FRONTIER 2 studies informed dose selection for the ICO Phase 3 PsO program:

- **Estimates from ER models based on $C_{avg,\,ss}$ indicated that ICO 200 mg QD would provide similar clinical response rates up to W52 as 100 mg BID in participants with moderate-to-severe plaque PsO**
- **ICO 200 mg QD modeling indicated durable response rates for clear/almost clear and clear skin**

Analyses & Results

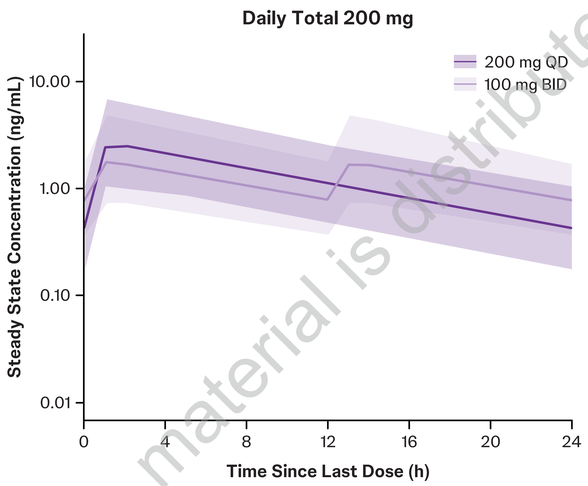
Population pharmacokinetic (PK) analyses

- Performed using integrated data from Phase 1 (healthy volunteers) and Phase 2 studies (participants with moderate-to-severe plaque PsO receiving oral ICO 25 mg QD, 25 mg BID, 50 mg QD, 100 mg QD, or 100 mg BID)
- Described using a one-compartment model with first-order absorption and linear elimination
- Relationship between clinical response and population PK-predicted average concentration (C_{avg}) was modeled via ordinal logistic regression

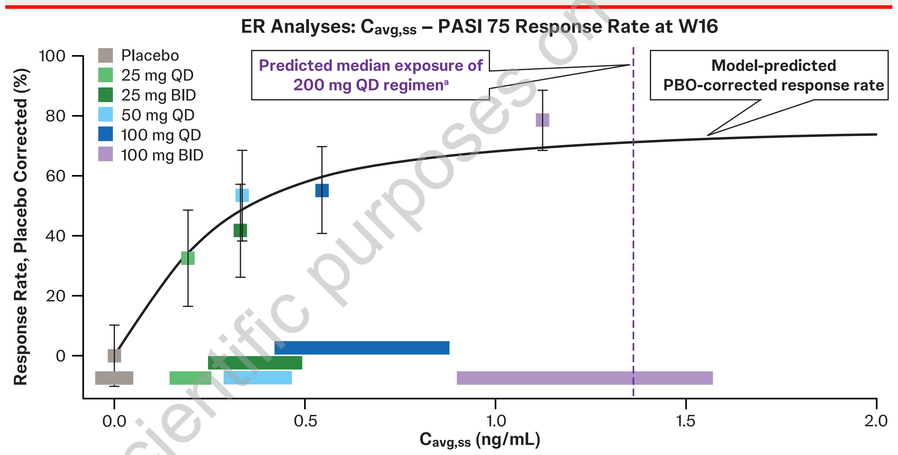
Exposure-response (ER) analyses

- Dataset included individual PK exposure metrics and PASI/IGA data from 231 participants, including the PBO group
- Missing clinical response data were treated as missing and not imputed
- As the study had no placebo control after W16, placebo response rates at W16 were carried forward to W24 and W52
- Observed and model-predicted PBO-corrected response rates were plotted versus C_{avg} at steady-state ($C_{avg,ss}$)

Overall exposures were similar between ICO 200 mg QD and 100 mg BID at steady-state

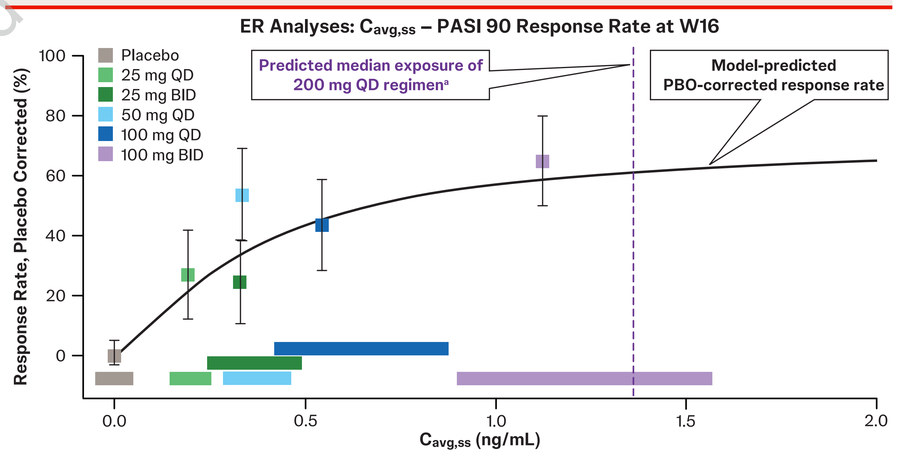


W16 ER showed a strong signal and indicated ICO 200 mg QD would achieve a similar PASI 75 response rate as 100 mg BID



$C_{avg,ss}$ is average ICO concentration at steady-state based on population PK modeling. [a]Based on population PK model from 1000 simulated participants similar to those from the study; horizontal colored bars represent 25th-75th percentile of PK post-hoc exposure metrics of each dosing regimen. The boxes and whiskers represent the observed, PBO-corrected, response rates and corresponding 95% confidence intervals.

W16 ER showed a strong signal and indicated ICO 200 mg QD would achieve a similar PASI 90 response rate as 100 mg BID



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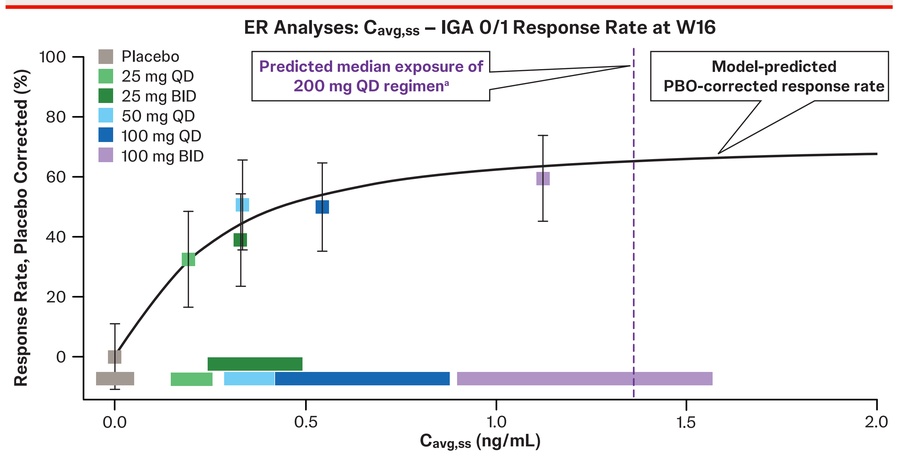
W16 ER showed a strong signal and indicated ICO 200 mg QD would achieve a similar IGA 0/1 response rate as 100 mg BID



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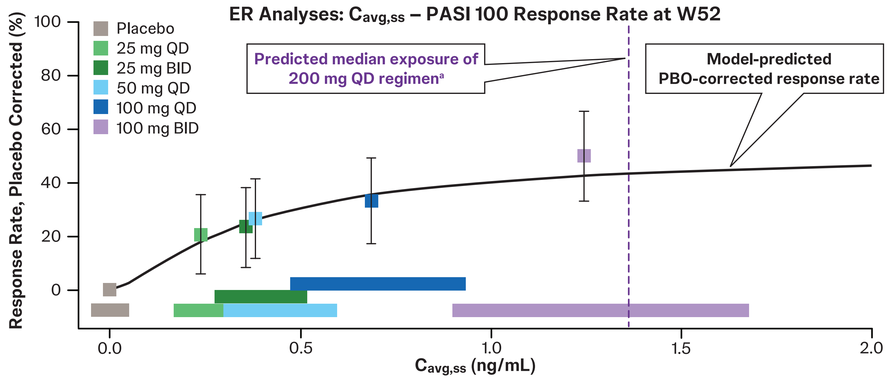
As explored by ER modeling, PBO-corrected PASI and IGA maximal response rates were maintained or increased from W16 to W24 and W52 (W52 PASI 100 shown)

- W16 ER also showed a signal and indicated ICO 200 mg QD would achieve a similar PASI 100 response rate as 100 mg BID



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