Pharmacokinetic Bridging of Icotrokinra (JNJ-77242113) Oral Solution and Tablet Formulations

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Background

The interleukin (IL)-23 pathway plays a key role in the pathogenesis of psoriasis (PsO), psoriatic arthritis (PsA), and inflammatory bowel disease (IBD)[1]

Inhibition of IL-23 signaling via monoclonal antibodies has demonstrated efficacy and safety in patients with psoriatic disease[2] and IBD[3]

Icotrokinra (formerly JNJ-77242113)

- A first-in-class, targeted oral peptide that inhibits IL-23 signaling by binding to the IL-23 receptor (R)
- Induced selective IL-23 pathway inhibition in *in vitro* and preclinical models, and showed pharmacodynamic activity in healthy human volunteers[4]
- In late-stage clinical trials for the treatment of inflammatory diseases
- Demonstrated significant, skin clearance and no safety signals through 1 year in Phase 2 PsO studies[5,6] and through 24 weeks in a Phase 3 PsO study[7]

Objectives

Compare the pharmacokinetic (PK) parameters and bioavailability of icotrokinra oral formulations across development phases:

- **1x100 mg tablet (PsO Phase 2) vs 100 mg solution (first-in-human; FIH)**
- **2x100 mg tablet (PsO Phase 2) vs 1x200 mg tablet (PsO Phase 3)**

Methods

Icotrokinra Phase 1 study designs

EudraCT 2021-003440-24	EU CT 2023-504720-26
Open-label, **single-dose**, randomized, crossover Phase 1 study	Open-label, **single-dose**, randomized crossover Phase 1 study
Icotrokinra formulations[a] 1x100 mg tablet (PsO Phase 2) vs 100 mg solution (FIH)	**Icotrokinra formulations**[a] 2x100 mg tablet (PsO Phase 2) vs 1x200 mg tablet (PsO Phase 3)
Relative bioavailability, PK, safety and tolerability	**Relative bioavailability, PK**, safety and tolerability
N=14 healthy volunteers, **fasted**	N=24 healthy volunteers, **fasted**

[a]Washout period of at least 7 days between the study intervention administrations of each individual participant.

PK assessments and analyses

- **PK samples:**
  - Blood samples collected over 48 h post-dose
  - Plasma samples were analyzed using a validated, specific, and sensitive LC-MS/MS method
- **PK parameters were calculated from plasma concentration-time data by noncompartmental analysis using Phoenix™ WinNonlin® 8.3 (Certara LP)**
- **PK parameters used to evaluate relative bioavailability were C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$:**
  - Log transformed PK parameters were analyzed using a mixed effect model with treatment, sequence, and period as fixed effects, and participant in sequence as a random effect. Results were back-transformed to the normal scale
  - GMRs were assessed
  - Intra-participant CV (%) was calculated as 100*(√(exp(mean square error)-1)

$AUC_{0\text{-}last}$=area under the plasma concentration-time curve from time zero to the time of the last measurable concentration; $AUC_{0\text{-}\infty}$=AUC from time zero extrapolated to infinity; C_{max}=maximum plasma concentration; CV=coefficient of variation; GMR=geometric mean ratio; h=hour; LC-MS/MS=liquid chromatography with tandem mass spectrometry.

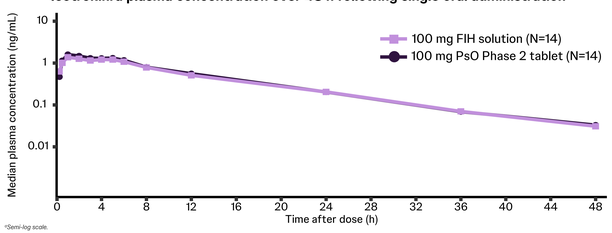
Key Takeaways

- **Icotrokinra is a first-in-class, targeted oral peptide in late-stage clinical development for the treatment of inflammatory diseases, such as PsO, PsA, and IBD**
- **Oral FIH icotrokinra solution and PsO Phase 2 tablet formulations had comparable PK and bioavailability**
- **Oral PsO Phase 2 and Phase 3 icotrokinra tablet formulations also had comparable PK and bioavailability**
- **PK bridging was established between the different phases of clinical development for icotrokinra**

Results

Icotrokinra plasma concentrations were comparable across oral FIH solution and PsO Phase 2 tablet formulations

Icotrokinra plasma concentration over 48 h following single oral administration[a]



[a]Semi-log scale.

Icotrokinra showed comparable PK parameters across oral FIH solution and PsO Phase 2 tablet formulations

Plasma PK of icotrokinra following single oral administration

Parameter	100 mg FIH solution (N=14)	100 mg PsO Phase 2 tablet (N=14)
C_{max}, ng/mL	2.04 (1.06)	2.10 (0.94)
t_{max}, h	1.01 (0.25-5.02)	2.51 (0.25-5.00)
$t_{1/2}$, h	8.9 (1.9)	8.7 (0.9)
$AUC_{0\text{-}last}$, h*ng/mL	20.5 (6.8)	21.9 (8.3)
$AUC_{0\text{-}\infty}$, h*ng/mL	21.0 (6.7)	22.3 (8.3)

Data presented as mean (SD) or median (min – max). SD=*standard deviation;* $t_{1/2}$=*plasma elimination half-life;* t_{max}=*time to reach maximum plasma concentration.*

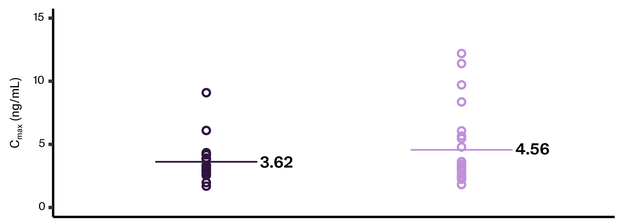
Extent of icotrokinra absorption was similar for the oral PsO Phase 2 tablet vs FIH solution formulations

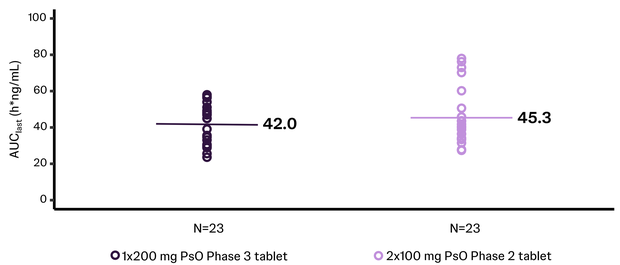
Comparison of PK parameters of icotrokinra following single oral administration

Parameter	Geometric mean: 100 mg FIH solution (N=14)	Geometric mean: 100 mg PsO Phase 2 tablet (N=14)	GMR[b], %	90% CI, %	Intra-participant CV, %
C_{max}, ng/mL	1.83	1.95	106.4	84.0-134.8	37.8
$AUC_{0\text{-}last}$, h*ng/mL	19.9	21.0	105.6	90.6-123.1	24.0
$AUC_{0\text{-}\infty}$, h*ng/mL	19.9[a]	21.8[a]	109.7	94.4-127.4	22.5

[a]N=13. [b]Test=100 mg PsO Phase 2 tablet and reference=100 mg FIH solution. CI=confidence interval.

Mean AUCs of icotrokinra were similar across the oral PsO Phase 2 and Phase 3 tablet formulations

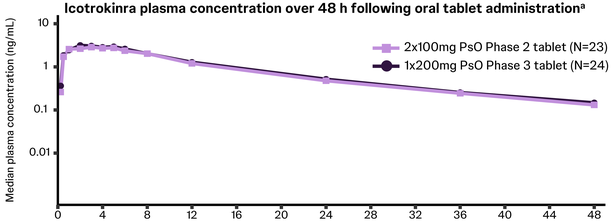




Cross marks represent means.

Plasma concentration profiles were similar between the oral PsO Phase 2 and Phase 3 tablet formulations

Icotrokinra plasma concentration over 48 h following oral tablet administration[a]



[a]Semi-log scale.

Icotrokinra showed generally comparable PK parameters across the oral PsO Phase 2 and Phase 3 tablet formulations

Plasma PK of icotrokinra following oral tablet administration

Parameter	2x100 mg PsO Phase 2 tablet (N=23)	1x200 mg PsO Phase 3 tablet (N=24)
C_{max}, ng/mL	4.56 (3.05)	3.62 (1.48)
t_{max}, h	2.00 (0.25 - 5.00)	2.00 (0.25 - 8.00)
$t_{1/2}$, h	12.4 (3.5)	13.0 (4.1)
$AUC_{0\text{-}last}$, h*ng/mL	45.3 (15.5)	42.0 (10.7)[a]
$AUC_{0\text{-}\infty}$, h*ng/mL	47.9 (16.0)	44.8 (11.4)[a]

Data presented as mean (SD) or median (min – max). [a]N=23.

Icotrokinra absorption was similar for the oral PsO Phase3 tablet vs Phase 2 tablet formulations

Comparison of PK parameters of icotrokinra following single oral administration

Parameter	Geometric mean: 2x100 mg PsO Phase 2 tablet (N=23)	Geometric mean: 1x200 mg PsO Phase 3 tablet (N=24)	GMR[b], %	90% CI, %	Intra-participant CV, %
C_{max}, ng/mL	3.86	3.40	88.1	74.3-104.4	35.6
$AUC_{0\text{-}last}$, h*ng/mL	43.7	41.1[a]	94.2	85.1-104.3	20.5
$AUC_{0\text{-}\infty}$, h*ng/mL	46.2	43.8[a]	94.9	85.6-105.2	20.7

[a]N=23. [b]Test=1x200 mg PsO Phase 3 tablet and reference=2x100 mg PsO Phase 2 tablet.

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