# PopPK and PKPD Modeling of an Oral NLRP3 Inhibitor Supporting Dose Simulation in Parkinson's Disease

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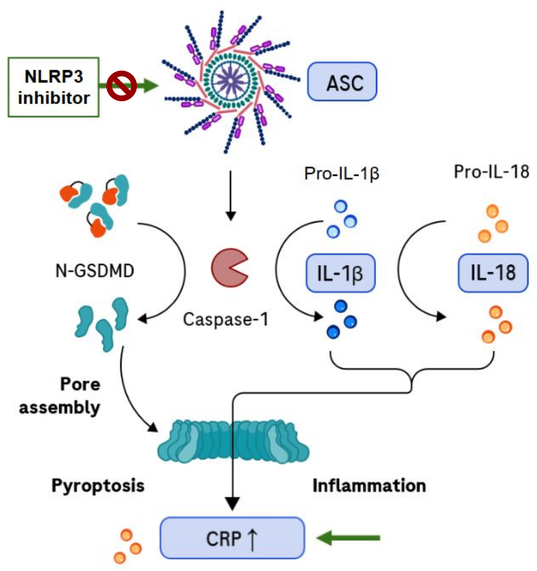
## Background & Objectives

🔥 Inflammatory Pathway (Fig 1)
**N**ucleotide-binding oligomerization domain, **L**eucine **R**ich repeat and **P**yrin domain containing **3** (**NLRP3**) inflammasome drives release of interleukin (IL)-18 and IL-1β [1,2]
NLRP3 inhibition is relevant in:
🛡️ Peripheral inflammatory diseases,
🧠 Neurodegenerative diseases, possibly via microglial activation [3,4,5]

💊 Therapeutic targeting of NLRP3
Selective & reversible inhibitor: oral small-molecule selnoflast (RG6418)

🎯 Objectives
Characterize selnoflast PK, PK-ex vivo stimulated IL-1β (PK-IL-1β) and PK-hsCRP and simulate the expected pharmacologic response across a range of doses.
This was mainly based on the data from a Phase Ib study to test the safety, PK/PD of selnoflast in early-stage Parkinson's disease

**Fig 1 NLRP3 priming and activation**




*ASC, Apoptosis-associated speck-like protein containing a CARD; N-GSDMD, N-terminal domain of Gasdermin D; CRP, C-reactive protein*

## Methods

👥 Populations and data: only active arms were included (Table 1 and Fig 2)

**Table 1 Populations and data**

| Study | Dose, mg; Days | N | PK Samples, n | PK times, h | IL-1β; hsCRP Samples, n | IL-1β & hsCRP times, h |
|---|---|---|---|---|---|---|
| Healthy volunteers [6] | SAD 20-600<br>MAD: 180–450 OD; 7 | 52 | 1114 | Every 12 h + 0-24 h; Day 1, 7 | - | - |
| Ulcerative Colitis [6] | 450 QD; 7 | 13 | 233 | Trough + 0-10 h; Day 1, 5 | - | - |
| Parkinson's Disease | 200 BID; 28 | 39 | 605 | Trough + 0-8 h; Day 1, 15, 28 | 188; 294 | 0, 2 h; Day 1, 15, 28 |

SAD, single ascending dose; MAD, multiple ascending dose; BID, twice daily; OD, once daily; N, number of participants; PK, pharmacokinetics.

⚙️ Base Models
Software: nonlinear mixed-effect modeling NONMEM 7.4.3 [7]
PopPK: 1- & 2-compartment with first-order absorption ± lag time or transit compartment models (± depot)
PopPK-IL-1β & -hsCRP: direct, indirect, or effect compartment. Linear, or Emax relationship

🔍 Covariates & Model Evaluation
Covariates investigated: bodyweight, food, age, creatinine clearance, race, and sex
Model evaluation: prediction-corrected visual predictive checks (pVPCs) and Sampling Importance Resampling (SIR) [8,9]

💻 Dose Simulation
Shiny app based on the final models was used to simulate ex vivo stimulated IL-1β in the whole blood and downstream biomarker (hsCRP) across a range of doses

## Results

⚙️ Base PopPK Models (Fig 3)
One compartment model with six transit absorption compartments and 1st-order elimination
IIV on CL, V, transit rate; IOV on transit rate. Combined error model and allometric scaling [10]
⚙️ Base PopPK-IL-1β and PopPK-hsCRP Models (Fig 3)
Ex-vivo stimulated IL-1β release: Direct Emax model with IIV on EC90 & baseline
hsCRP: Indirect Emax model with IIV (full block) on EC50 & baseline

🔍 Covariates & Model Evaluation
Food ↓ transit absorption rate by 66%
Clearance ↓ with age: ~13% lower at 65 vs 40 years
Good predictive performance (Fig 4) and relative standard errors of less than 35% (Table 2)
Relatively large proportional error in the PopPK-IL-1β due to biological variability of the assay

**Fig 2 Selnoflast plasma concentrations, whole blood ex-vivo stimulated IL-1β and plasma hsCRP in Parkinson's Disease**

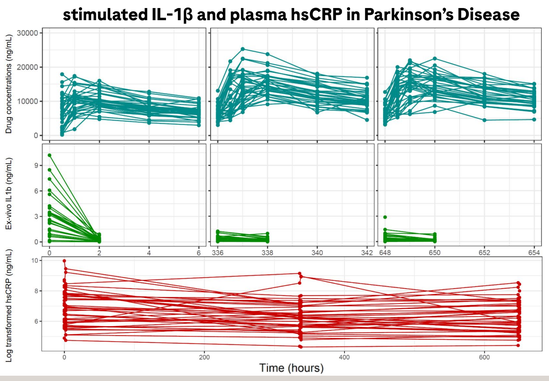



**Fig 3 PopPK PK-IL-1β and PK-hsCRP models structure**

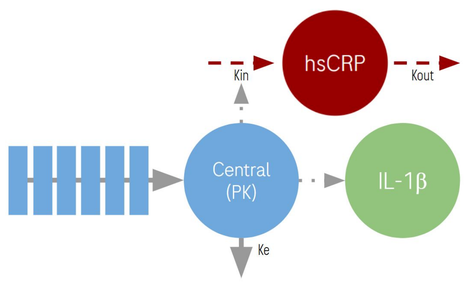


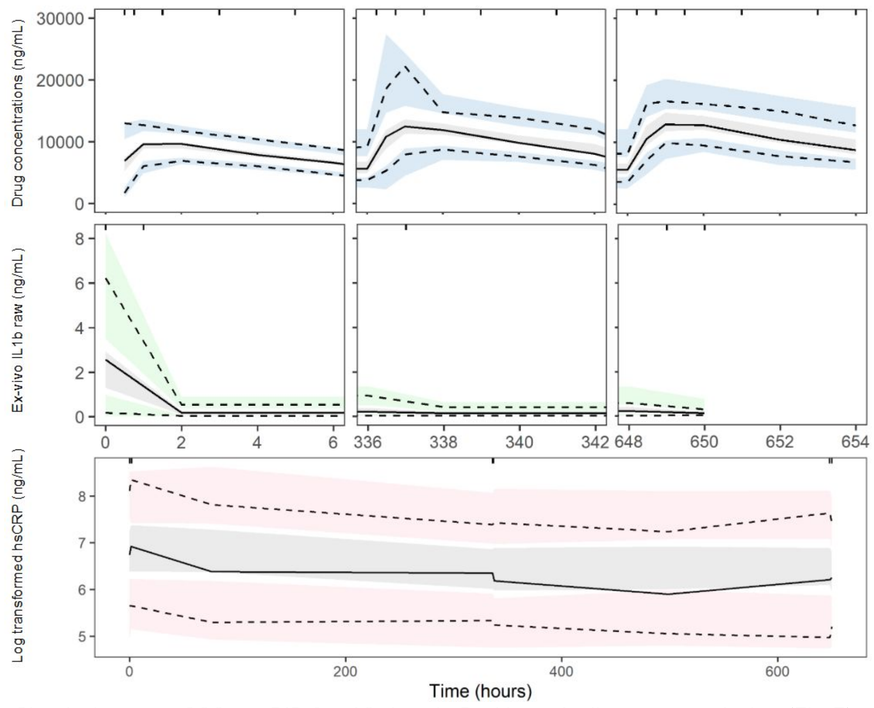

**Table 2 Summary of parameter estimates in the final PopPK and PKPD models**

| PopPK Parameter (unit) | Estimate | RSE (%) | IIV (%) | RSE (%) |
|---|---|---|---|---|
| Clearance, CL (L.hr$^{-1}$) | 1.66 | 2.1 | 21.8 | 6.9 |
| Volume of distribution, V1 (L) | 16.8 | 1.2 | 11.2 | 7.5 |
| Rate of transit absorption, KTR (hr$^{-1}$) | 12.1 | 3.6 | 23.5 | 14.3 |
| IOV in KTR (%) | 38.5 | 6.8 | - | - |
| Age effect on clearance | -0.285 | 16.1 | - | - |
| Food effect on KTR | -0.659 | 3.2 | - | - |
| Proportional error (%) | 17.4 | 1.0 | - | - |
| Additive error (ng/mL) | 35.9 | 13.0 | - | - |

| PopPK-IL-1β Parameter (unit) | Estimate | RSE (%) | IIV (%) | RSE (%) |
|---|---|---|---|---|
| Baseline (ng/mL) | 2.2 | 15.2 | 61.3 | 16.4 |
| EC90 (ng/mL) | 7640 | 13.5 | 48.0 | 32.1 |
| Proportional error (%) | 61.8 | 6.4 | - | - |

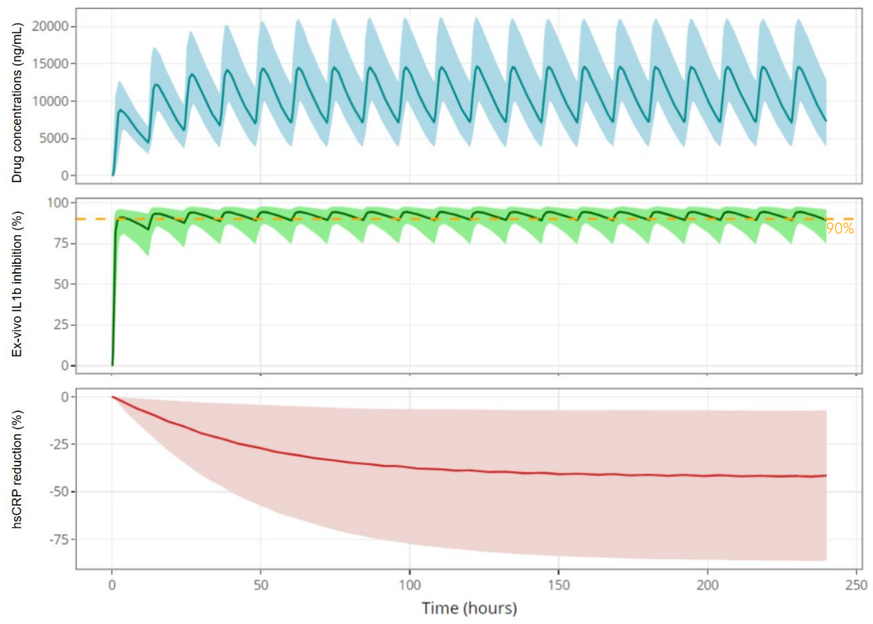
| PopPK-hsCRP Parameter (unit) | Estimate | RSE (%) | IIV (%) | RSE (%) |
|---|---|---|---|---|
| Baseline (ng/mL) | 956 | 12.3 | 86.1 | 8.6 |
| EC50 (ng/mL) | 16500 | 31.6 | 140 | 15.0 |
| Effect half-life (h) | 30.5 | 31.8 | - | - |
| Proportional error (%) | 47.5 | 1.5 | - | - |

**Fig 4 pcVPCs of the PopPK and PKPD models in Parkinson's disease (solid and dashed lines are the median, 10th and 90th of observed data; shaded area are 95% confidence intervals of the simulated data**




💻 Dose Simulation: e.g, 200 mg BID for 10 days in Parkinson's disease population (Fig 5)
~90% median ex-vivo stimulated IL-1β inhibition maintained at C-trough
~45% unadjusted reduction in hsCRP

**Fig 5 Simulated selnoflast (200 BID) concentrations in Parkinson's disease population, ex vivo stimulated IL-1β and hsCRP for 10 days (solid lines are median of simulated data; shaded areas are 95% prediction intervals)**




## Conclusions

The developed PopPK, PopPK-IL-1β and PopPK-hsCRP modeling framework for the NLRP3 inhibitor selnoflast successfully integrated PK and Parkinson's Disease biomarker data, with the aim to predict ex vivo stimulated IL-1β inhibition in the whole blood and plasma hsCRP reduction for future clinical studies with NLRP3 inhibitors.

## References

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