Population pharmacokinetic-pharmacodynamic modeling of the iclepertin drug effect on hemoglobin levels

Nina Hanke [1], Peter Nagy [2], Corey Reuteman-Fowler [3], Mahmoud Tareq Abdelwahab [1], Samuel P Callisto [4], Fredrik Gruenenfelder [2], Michael Desch [1]

[1] Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [2] Boehringer Ingelheim International GmbH, Ingelheim, Germany; [3] Boehringer Ingelheim Pharma Inc., Ridgefield, CT, USA; [4] Metrum Research Group, Tariffville, CT, USA

Objectives

1. Develop a population pharmacokinetic-pharmacodynamic (popPKPD) model to describe and predict the impact of iclepertin exposure on patient hemoglobin levels
2. Simulate the hemoglobin concentration-time course under chronic iclepertin treatment (365 days) to see if there will be a new hemoglobin steady-state and when this will be reached
3. Assess the hypothetical risk of anemia for the worst-case scenario iclepertin exposure

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Introduction

- Iclepertin (BI 425809) is a novel, potent and selective glycine transporter-1 (GlyT1) inhibitor currently in Phase III development to help patients with cognitive impairment associated with schizophrenia (CIAS).
- Inhibition of GlyT1 in the presynaptic membranes increases the glycine concentration in the synaptic cleft, to enhance N-methyl-D-aspartate (NMDA) receptor signaling and is hypothesized to improve cognitive function and memory.
- However, glycine is also required for the first step of heme biosynthesis in the red blood cells. While inhibition of GlyT1 in the brain aims to improve cognition in schizophrenia patients, inhibition of GlyT1 in the cell membrane of erythrocyte precursors could possibly interfere with glycine uptake and heme biosynthesis, and consequently affect the production of hemoglobin.

Methods

- The model was developed based on data from 3 clinical iclepertin studies (n=25 healthy volunteers, n=599 Alzheimer's Disease Dementia patients, n=492 Schizophrenia patients, EudraCT Numbers: 2014-005652-26, 2015-005438-24, 2016-000285-28), and a literature model describing the effect of the discontinued Roche GlyT1 inhibitor bitopertin on hemoglobin levels [1]. A previously developed popPK model was used to predict individual steady-state iclepertin exposure for all study participants (AUCss) [2]. The predicted PK exposure was then used in the popPKPD iclepertin-hemoglobin model to drive the iclepertin drug effect.
- Blood hemoglobin concentrations (the investigated safety marker) are the product of mean corpuscular hemoglobin (MCH, hemoglobin mass per red blood cell) and the red blood cell count per liter (RBC). The model was developed by simultaneously fitting to both MCH and RBC observations. This allowed quantification of the impact of iclepertin GlyT1 inhibition on hemoglobin synthesis within the red blood cells (affecting the MCH production rate), and incorporation of the physiological feedback from changes in hemoglobin levels that regulate the red blood cell production (affecting the RBC production rate).
- Non-linear mixed-effects modeling and simulation were conducted with NONMEM 7.4.3, PsN 4.8.1 and mrgsolve in R 3.5.3.

Results – Model structure

- The current best model consists of two parallel chains of 4 transit compartments each, representing the production, lifespan, and elimination of the red blood cells (RBC) with their hemoglobin content (MCH).
- GlyT1 inhibition by iclepertin was implemented as proportional drug effect via an Emax relationship on the MCH production rate. The physiological hemoglobin feedback mechanism that stimulates RBC synthesis in response to tissue hypoxia was modelled as a power function based on the relative hemoglobin change from baseline on the RBC production rate.
- The identified covariates are: sex, age, body mass index, race and liver function. No significant impact of kidney function could be identified.

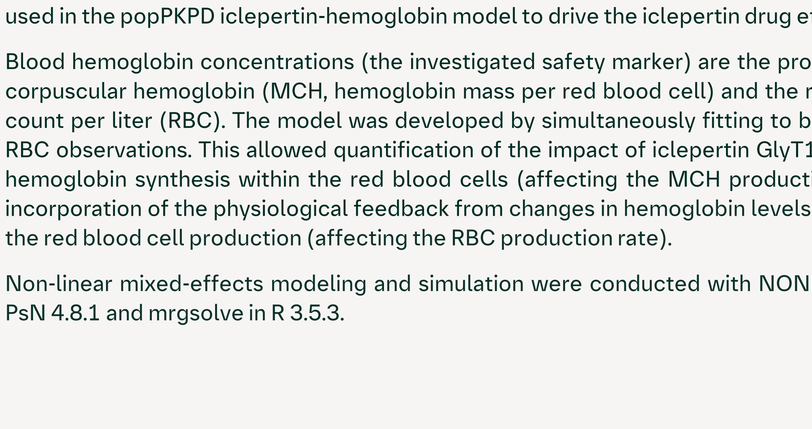

Figure 1. Iclepertin drug effect on hemoglobin levels, current best model structure.

Results – Model evaluation

- All parameters were estimated with good precision (<30% RSE). Goodness-of-fit plots, individual fits and visual predictive checks all demonstrate good model performance for MCH and for RBC.

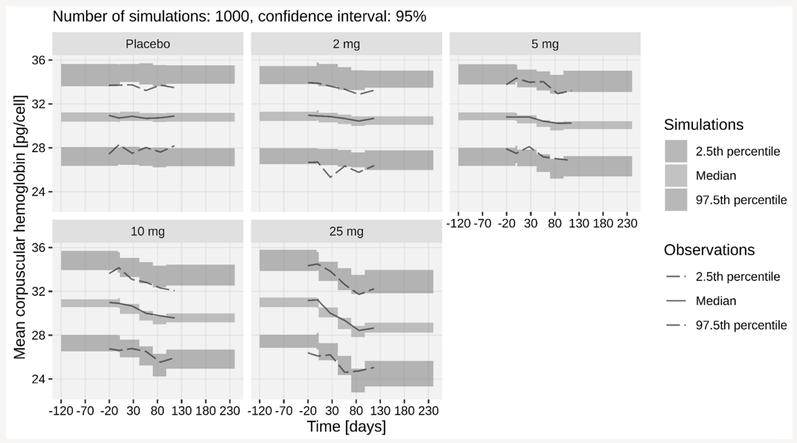

Figure 2. Visual predictive checks of MCH levels in the Alzheimer's patient Phase II study, stratified by iclepertin dose group (Placebo: n=118, 2 mg: n=120, 5 mg: n=118, 10 mg: n=122, 25 mg: n=121). Shaded areas: 95% confidence intervals for simulated medians, 2.5th and 97.5th percentiles. Lines and dashed lines: aggregated observed medians, 2.5th and 97.5th percentiles.

Results – Safety

- Simulations show a decreased hemoglobin steady-state under chronic iclepertin treatment, reached after approximately 120-140 days.
- For a typical patient, the projected therapeutic dose of 10 mg iclepertin daily is predicted to decrease hemoglobin by 2.0%.
  The potential worst-case scenario of 5-times increased iclepertin exposure due to co-administration of a strong CYP3A4 inhibitor is predicted to decrease hemoglobin by 7.6%.
- Even for this worst-case scenario, at least 95% of the virtual patients stay above the defined hemoglobin safety thresholds of 100 g/L for women and 110 g/L for men.

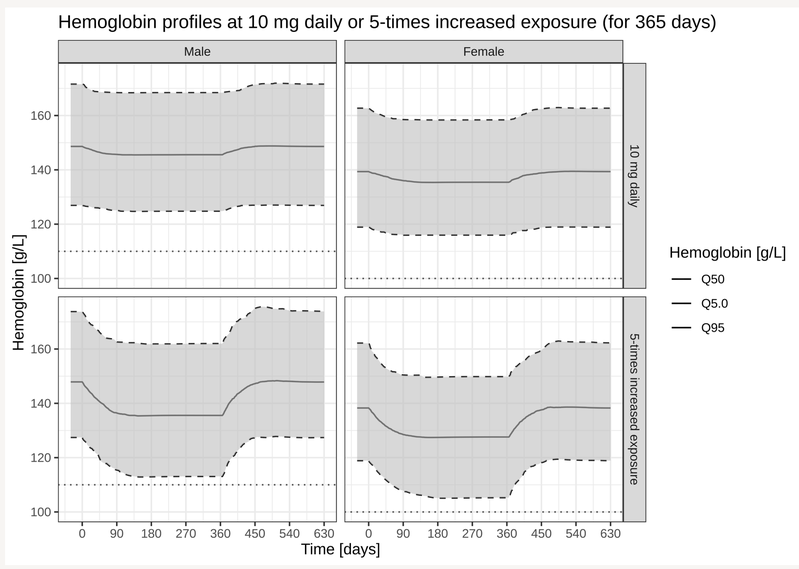

Figure 3. Population simulations of the hemoglobin concentration-time profiles during chronic iclepertin treatment (365 days). Solid and dashed lines: population medians, 5th and 95th percentiles. Dotted lines: hemoglobin safety thresholds (100 g/L for women, 110 g/L for men).

Conclusions

- A popPKPD model to describe and predict the impact of iclepertin exposure on patient hemoglobin levels was successfully developed.
- Simulations predict new (lower) hemoglobin steady-state levels under chronic iclepertin treatment that are reached after approximately 120-140 days.
- At the projected clinically-relevant exposures (corresponding to 10 mg iclepertin daily, up to the worst-case scenario of 5-times increased exposure), population simulations predict that at least 95% of the patients will stay above the hemoglobin safety thresholds.

References
[1] Schaedeli Stark et al. 2012. PAGE 21 Abstract 2553 [www.page-meeting.org/?abstract=2553]
[2] Callisto et al. 2021. Internal Report c36250553

Abbreviations
ALT, alanine transaminase; AUCss, area under the curve at steady-state; BMI, body mass index; CIAS, cognitive impairment associated with schizophrenia; GlyT1, glycine transporter-1; Kin_MCH, MCH production rate; Kin_RBC, RBC production rate; Ktr, transit compartment transfer rate; MCH, mean corpuscular hemoglobin (pg/cell); NMDA, N-methyl-D-aspartate; popPKPD, population pharmacokinetic-pharmacodynamic; RBC, red blood cell count (cells/L); RSE, relative standard error

Conflict of interest
This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.
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