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Pharmacokinetics, Pharmacodynamics and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients

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Abstract

Population pharmacokinetic (popPK) modeling was used to characterize the PK profile of the oral janus kinase (JAK)1/JAK2 inhibitor, baricitinib, in 18 patients with Mendelian interferonopathies who are enrolled in a compassionate use program. Patients received doses between 0.1 to 17 mg per day. Covariates of weight and renal function significantly influenced volume-of-distribution and clearance respectively. The half-life of baricitinib in patients less than 40kg was substantially shorter than in adult populations, requiring the need for dosing up to 4 times daily. On therapeutic doses, the mean area-under-the-concentration-versus-time curve was 2388 nM*hr, which is 1.83-fold higher than mean baricitinib exposures in adult patients with rheumatoid arthritis receiving

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AUTHOR CONTRIBUTIONS

H.K., K.M.B., P.K., and R.G.M. wrote the manuscript; X.Z., W.L.M., and R.G.M. designed the research; M.B., S.R.B., G.M.S., A.A.J., H.K., Y.H., W.L.T., and M.G. performed the research; H.K., K.M.B., P.K., C.C.T., A.P., P.W., X.Z., and R.G.M. analyzed the data; A.P., X.Z., P.W., and J.M.J. contributed new reagents/analytical tools.

doses of 4mg once-daily. Dose-dependent decreases in interferon (IFN) biomarkers confirmed an *in vivo* effect of baricitinib on type-1 IFN signaling. PopPK and PD data support a proposal for a weight- and eGFR-based dosing regimen in guiding baricitinib dosing in patients with rare interferonopathies.

TRIAL REGISTRATION. NCT01724580, NCT02974595

Keywords

Baricitinib pharmacokinetics; monogenic interferonopathies; CANDLE; SAVI; compassionate use treatment program

Introduction

Expanded access, or "compassionate use," programs provide patients with poor treatment options, for whom a clinical trial is not available or possible, with access to potentially beneficial investigational drugs. However, dosing information in special populations, such as pediatric patients, may not be available at the onset of such a program, posing challenges in dosing optimization and safety monitoring.

An FDA-approved compassionate use program (NCT01724580) was initiated in 2011 for the treatment of pediatric patients with rare Mendelian autoinflammatory diseases (AIDs) with presumed interferon (IFN)-mediated pathology.^{1, 2} Patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE), caused by loss-of-function mutations in proteasome components,^{3–7} and later Stimulator of interferon genes (STING)-associated vasculopathy with onset in Infancy (SAVI), which is caused by gain-of-function mutations in the viral sensor and adaptor molecule *TMEM173*/STING, were included. IFN-mediated AIDs are characterized by chronic sterile systemic and organ-specific inflammation and a chronically elevated IFN-response-gene signature (IRS) in the blood.^{1, 8, 9}

Chronically elevated IRS in the blood of CANDLE and SAVI patients suggested a role of increased IFN signaling in causing the disease manifestations of CANDLE and SAVI, and prompted the compassionate use treatment with a novel class of drugs, Janus kinase (JAK) inhibitors. The JAK/Signal Transducers and Activators of Transcription (STAT) pathway constitutes a principal signaling pathway for a number of cytokine and growth factor receptors, including the IFN α/β receptor (IFNAR) and the IFN γ receptor (IFNGR).^{10–12} JAK inhibitors reduce Type-I and Type-II IFN-induced STAT-1 phosphorylation (pSTAT1) *in vitro*,^{10, 13} which suggested their potential utility in reducing the IFN signaling and in potentially improving treatment outcomes in IFN-mediated AIDs, including patients with CANDLE and SAVI who poorly responded to available conventional and biologic disease-modifying antirheumatic drugs (DMARDs), and an estimated 30% of patients with poor treatment responses do not survive to adulthood.⁹

Population pharmacokinetic (PopPK) modeling was used to analyze pharmacokinetic (PK) data that were collected under the compassionate use program in patients with CANDLE

and SAVI. PopPK modeling allows the analysis of sparse PK data in the context of blood volume constraints, ethical concerns and safety concerns in obtaining frequent PK samples in a pediatric population that would otherwise be required to generate a full PK profile.^{14, 15} The effect of baricitinib on IFN biomarkers, including IFN α -stimulated STAT-1 phosphorylation (pSTAT1), IP-10 serum levels and a 25-gene, whole-blood, IFN response gene signature was also assessed. The analyses performed supported the development of an oral dosing regimen based on clinically effective doses that may guide the use of baricitinib in patients with CANDLE, SAVI, and other rare interferonopathies.

RESULTS

Patients

Between October 2011 and February 2016, 18 patients were enrolled into a compassionate use program and underwent serial PK assessments. The mean age at enrollment was 12.5 years (range 1.2–24.1); 66.7% were male and 88.9% were white (Table 1). Weight at enrollment ranged from 9.2 to 84.3 kg, with a median weight of 25.5 kg. Ten patients had genetically confirmed CANDLE, 4 patients had genetically confirmed SAVI and 4 patients had other presumed interferonopathies referred to as CANDLE-related conditions, as diagnosed by the investigators.

The mean duration of baricitinib treatment was 2.4 years (SD ± 1.1 year) at the final PK assessments. Baricitinib doses given throughout the clinical program ranged from 0.01 to 0.82 mg/kg/day (0.1 to 17 mg/day). The mean ($\pm$ SD) baricitinib dose after the final PK visit included in the analysis was 8.1 ± 2.4 mg/day (0.24 ± 0.13 mg/kg/day). Doses were administered either as single or divided doses up to 4–5 times daily, in the lowest weight group, depending on the patient's weight, clinical response, and safety measures. Drug doses started at 100 mcg/day and were escalated if patients had a partial response and PK parameters were within boundaries measured in adult patients with rheumatoid arthritis (Supplementary Methods). PK analyses were performed on clinically effective doses (manuscript submitted).

Baricitinib PK is significantly influenced by weight and renal function in interferonopathy patients

PopPK analysis was performed with the sparse PK data obtained from the 18 patients enrolled into this compassionate use program. A total of 538 measurable concentrations were collected between November 2011 and March 2016. The final model, which included 522 concentrations (see Supplementary Methods for detail), comprised a one-compartment model with zero-order absorption. Model diagnostic plots based on goodness-of-fit and predictive checks can be reviewed in Figures S1 and S2 and the Supplementary Methods. The model adequately described baricitinib disposition characteristics, as the majority of observed concentrations fell within the modeled 95% prediction intervals.

PopPK parameter estimates are presented in Table 2. Body weight and renal function (measured by estimated glomerular filtration rate [eGFR]) were significant covariates on the volume of distribution (V/F) and clearance (CL/F), respectively (Figure 1). The V/F

correlated reasonably with BSA (data not shown) and weight, thus all PK parameters and dosing recommendations were stratified by weight (Tables 3, and 4). Values of 20 kg and 40 kg were selected as reasonable cut-offs for weight categories to stratify reporting of key PK parameters. PK parameters differed in weight-matched patients when eGFRs fell below 120 mL/min/1.73 m², which led to further stratification by eGFRs above and below this threshold (Tables 3, and 4).

In patients with eGFRs $\geq$ 120 mL/min/1.73 m², the mean drug exposure over a 24-hour interval (area-under-the-concentration-time curve over 24 hours at steady state [AUC_{24,ss}]) at the final therapeutic dose was 2580 (CV 12.6%), 2020 (CV 20.2%), and 1940 (CV 39.0%) nM*hr for weight categories of <20, 20–40, and >40 kg, respectively. Normalization of AUC by dose (AUC_{24,ss}/Dose) resulted in mean exposures of 322, 292, and 193 nM*h/mg for the respective weight categories. The mean CL/F increased from 8.4 (CV 12.6%) to 9.2 (CV 36.6%) to 13.9 (CV 22.2%) L/h for weight categories of <20, 20 to 40, and >40 kg, respectively, but when corrected for weight (kg) the (CL/F)/kg was highest in children below 20kg, with a mean of 0.56 (CV 24.1%), 0.32 (CV 44.6%) and 0.22 (CV 29.5%) L/h/kg for weight categories of <20, 20 to 40, and >40 kg respectively (calculated from Table S1). Estimated half-lives (t_{1/2}) were 4.4 (CV 30.3%) and 5.0 (CV 44.0%) hours for weight categories of <20 kg and 20–40 kg, whereas a mean t_{1/2} of 7.0 (CV 37.4%) hours was estimated for the >40 kg category (Table 3). PK parameter estimates for individual patients are provided in Table S1.

Five patients (2 in the <20 kg and 3 in the >40 kg weight category) had eGFRs below 120 mL/min/1.73m² at the final PK visit. Compared to patients with eGFRs $\geq$ 120 mL/min/1.73m², the AUC_{24,ss}/Dose was ~52–59% higher in patients with eGFRs below 120 mL/min/1.72m² in the same weight-matched categories, with estimated t_{1/2} of 4.8 and 7.8 hours for patients <20 kg and >40 kg, respectively (Table 3).

Baricitinib decreases STAT-1 and STAT-3 phosphorylation (pSTAT-1 and pSTAT3) in patients' whole blood in a dose-dependent manner

To assess the effect of clinically effective baricitinib doses on the phosphorylation of STATs, we assessed IFN α -stimulated pSTAT-1 and IL-6-stimulated pSTAT-3 in 4 cell populations from peripheral blood at the time of PK profiling; pSTAT-1 and pSTAT-3 did not differ in CANDLE and SAVI patients (Figures 2A,B and Figures S3A,B). Baricitinib concentrations required to achieve 50% inhibition of IFN- α stimulated pSTAT-1 (IC₅₀ values) were 43.3 nM (95% CI: 18.9–67.6) for CD8+T cells and 51.1 nM (95% CI: 28.0–74.2) for CD4+ T cells. IC₅₀ values in CD14+ monocytes and CD19+ B cells were 137.7 nM (95% CI: 81.9–193.5), and 189.9 nM (95% CI: 165.8–214.1) respectively, and for monocytes were thus 3.2- and 2.7-fold higher compared to CD8+ and CD4+ T cells respectively (Figure 2A). Similarly, compared to CD8+cells, which had the lowest IC₅₀ values for IL-6 stimulated pSTAT-3, IC₅₀ values in monocytes were 1.8-fold higher than for CD8+ cells but 0.6-fold lower than in CD4+ T cells (Figure 2B).

We assessed pSTAT levels at baricitinib trough concentrations, before administration of the baricitinib morning dose, to determine whether median fluorescent intensity (MFI) ratios in patients returned to values measured in healthy controls during the dosing cycle. While

stimulated pSTAT-1 and pSTAT-3 did not significantly differ between healthy controls, the mean pSTAT-1 MFI ratios for CANDLE and SAVI patients were 1.3- to 1.6-fold reduced compared to the mean MFI ratios of healthy controls for all 4 cell types assessed (p -values <0.01 except for CD19+ B cells) (Figure 2C); mean pSTAT-3 MFI ratios in CD14+ monocytes and CD4+ T cell populations were 1.7- and 1.4-fold lower, respectively, compared to healthy controls (p -value <0.02), with no notable difference in CD8+ T cells (Figure S4).

25-gene whole blood IFN scores and serum IP-10 levels correlate with baricitinib exposure (AUC_{24,SS})

To assess the effect of baricitinib on downstream markers of IFN signaling, such as the reduction of the 25-gene IFN signature and on serum IP-10 levels, we calculated a 25-gene IFN score during protocol visits, and measured serum IP-10 concentrations from patients before baricitinib was administered in the morning. We observed a significant negative correlation for both the 25-gene IFN score and serum IP-10 levels, with increased drug exposure in all patients (Figure 3A,B). The inverse correlation was stronger for serum IP-10 levels than for the 25-gene IFN score, p -values <0.05 and <0.001). At target exposure levels of baricitinib AUC_{24,SS} between ~1500–2000 nM*h, a subset of CANDLE patients normalized their IFN scores (Figure 3A).

Safety data

At the time of the data analysis (October 2016), the mean duration of baricitinib exposure was 35.4 months (3.0 years), representing a total of 54 patient-years of exposure. No deaths have been reported during the program; however, two patients discontinued early due to adverse events, 1 patient with an undifferentiated interferonopathy discontinued due to osteonecrosis and failure to adequately respond after 14 weeks of baricitinib treatment, and 1 CANDLE patient discontinued baricitinib treatment due to renal tubulointerstitial disease in the context of high BK viremia titers, and was subsequently discontinued from the program due to acute kidney injury after 117 weeks of baricitinib treatment. These two patients succumbed to their underlying disease 18 and 4 months after discontinuation of baricitinib, respectively. Other viral infections included Herpes Zoster in 1 patient; BK viremia developed in 44% of patients, however viral titers remain low and stable on current treatment doses. As the clinical significance of low positive BK titers remains unclear, serum and urine BK titers and renal function are closely monitored in this patient population.

Proposal for an initial dosing regimen for baricitinib in patients with interferonopathies

The proposed dosing regimens (Tables 4 and 5) are based on drug doses that were tolerated and were considered to be clinically effective. At these doses IFN biomarkers dropped. The geometric mean AUC_{24,SS} value at clinically effective doses (i.e., at the final PK assessments) was ~2388 nM*h, and 5 CANDLE patients normalized their IFN scores for prolonged periods of time at AUC_{24,SS} values between ~1500 to 2000 nM*h (Figure 3A). Additionally, drug exposures reached in this patient population were assessed by interim PK analysis (see Supplementary Methods), primarily to ensure that estimated drug exposures with the proposed dosing regimen did not exceed the ranges that were tolerated in studies in adult populations.¹³

Based on the effect of renal function on PK parameters, we propose a dosing regimen for patients with “normal” renal function, defined as an eGFR ≥ 120 mL/min/1.73 m² and an adjusted dosing regimen for patients with an eGFR of <120 mL/min/1.73 m² (Table 4). Dosing recommendations are further stratified by weight categories within each table. The markedly shorter half-lives in pediatric patients, particularly in patients ≤ 40 kg, necessitated more frequent dosing in the 20–40 kg and <20 kg groups. The proposed initial baricitinib starting doses are projected to yield initial exposures ranging from 1769–2112, 1077–2688, and 1082–1958 nM·h for patients weighing <20 kg, 20–40 kg and >40 kg, respectively, with eGFRs ≥ 120 mL/min/1.73 m² (Table S2). In many patients, titrating to higher doses may be required to obtain optimal disease control; dosing increases with corresponding estimated drug exposures are detailed in Tables 4 and Table S2.

The lower baricitinib initial dosing regimen for patients with reduced renal function was derived from 5 patients with CANDLE or a CANDLE-related condition (2 with a weight of <20 kg and 3 patients with a weight of >40 kg). Dose-normalized drug exposure was approximately 52–59% higher than weight-matched patients with eGFRs ≥ 120 mL/min/1.73 m² (Table 3). For patients with eGFRs <120 mL/min/1.73 m², estimated exposures ranged from 1987–2120, 1374, and 733–2686 nM·h for starting doses in <20 kg, 20–40 kg and >40 kg weight categories, respectively (Table S2).

DISCUSSION

CANDLE and SAVI are two rare, orphan diseases with genetic and pathogenic data suggesting a role for chronic Type-I IFN signaling that causes an amplification of dysregulated immune cell and tissue responses. This signaling may contribute to chronic systemic and organ inflammation and damage. With no FDA-approved treatments, no defined standards of care, and poor disease outcomes due to a lack of effective treatment options, a compassionate use program with the JAK1/JAK2 inhibitor, baricitinib, was initiated in late 2011 as a potential therapeutic strategy to block the presumed Type-1 IFN feed-forward loop observed in this patient population and ameliorate disease symptoms. The absence of baricitinib dosing data in children led to the initial dependence on PK data from adult populations with RA and psoriasis, and on individualized PK assessments to monitor safety. Marked differences in drug elimination between this pediatric population and data in adults pointed to the need for a formal PK analysis.

We used PopPK analyses to characterize the PK profile and identified covariates that influenced baricitinib PK in this patient population. Consistent with adult PK data, baricitinib demonstrated dose linearity over a dosing range of 1–14 mg daily.¹³ A two-compartment model best fit the PK data in the adult population, whereas a one-compartment model best fit the data obtained in this predominantly pediatric population. The average half-life for baricitinib in our cohort is shorter, particularly in patients weighing ≤ 40 kg, than the reported estimates of 10 hours in healthy adult subjects, 12.8 hours in psoriasis patients, and 12.5 hours in the RA population.¹³ This observation supported the frequent dosing of baricitinib up to 4 times daily in patients weighing <20 kg in order to obtain AUC_{24,ss} estimates similar to those attained in patients weighing >40 kg.

The geometric mean $AUC_{24,SS}$ measured in this patient population at the final PK assessments was 2388 nM*h, which is 1.83-fold higher than the overall $AUC_{24,SS}$ value obtained in the RA population at once-daily doses of 4 mg which is estimated at 1304 nM*h (data on file, Eli Lilly and Company). The need for the higher dose requirements to achieve treatment efficacy in this population is likely due to the high clinical severity of the disease manifestations and extent of organ involvement. These observations are similar to those in patients with IL-1 mediated autoinflammatory syndromes (i.e., the cryopyrinopathies' disease spectrum), where higher drug concentrations are needed with increased disease severity to achieve adequate disease control.^{16–18} Furthermore, the pathogenic disease mechanisms in CANDIE and SAVI are thought to be caused by an amplified Type-I interferon signaling loop, which differs from putative disease mechanisms involving IL-6 and GM-CSF^{19, 20} and IL-22 signaling in RA and in psoriasis patients, respectively.²¹ The higher dose requirements in patients <20kg were likely related to the severe disease manifestations requiring a higher AUCs for patients in this weight group. Furthermore, ontogenic factors that include physiologic changes in body water, fat, and protein proportions, organ size and function, and changes in drug metabolizing enzymes/transporters that occur in infancy and childhood, can all affect drug metabolism including clearance and elimination^{22, 23}. In fact, observations that clearance (CL/F) by weight (kg) was highest in the lowest age and weight group support a role for ontogenic factors in influencing the pharmacokinetic profile.

Baricitinib is primarily renally cleared, and thus reductions in eGFR can reduce clearance and increase AUCs. Mild renal impairment (MDRD-eGFR of 60 to 90 mL/min/1.73 m²), did not increase AUC in comparison to normal renal function in otherwise healthy subjects, but moderate (MDRD-eGFR of 30 to 60 mL/min/1.73 m²) and severe (MDRD-eGFR <30 mL/min/1.73 m²) renal impairment increased baricitinib AUCs in the RA population 2-fold and 4-fold, respectively, and had only a minimal effect on C_{max} (data on file, Eli Lilly and Company). Notably, eGFR values below 120 mL/min/1.73 m² in this interferonopathy population were associated with higher dose-normalized AUCs in comparison to weight-matched patients with eGFRs ≥ 120 mL/min/1.73m². However, this is consistent with published data suggesting the need for higher eGFR cut-offs in pediatric patients for classifying renal impairment in comparison to adults.²⁴ While half-lives were similar between weight-matched categories of <20 kg with eGFRs above and below 120 mL/min/1.73 m², 1 patient (O3) in the >40 kg had eGFRs between 54–76 mL/min/1.73 m², and a corresponding prolonged estimated half-life of ~17–19.2 hours. Because only 5 patients had renal insufficiency, the interpretation of these data are limited, however pediatric patients with renal insufficiency should be monitored closely on baricitinib.

Baricitinib (LY3009104, also INCB028050) is a potent and selective small molecule that inhibits JAK1 and JAK2 signaling.²⁵ The *ex vivo* concentrations needed to block 50% of IFN α -mediated STAT-1 phosphorylation were lower in CD4+ and CD8+ T cells (51.1 and 43.3 nM, respectively) and higher in monocytes (137.7 nM) and were higher for blocking IL-6 mediated STAT-3 phosphorylation which is similar to reports from *in vitro* stimulation assays in healthy controls.^{13, 26} The suppression of IFN α -induced STAT-1 phosphorylation correlated with baricitinib serum levels and recovered to levels observed in healthy adults at times of drug trough levels. The baricitinib effect on STAT-1 phosphorylation did not

significantly differ between treated CANDLE and SAVI patients, but the effect on the reduction on the 25-gene IFN scores was more pronounced in CANDLE patients, which is likely influenced by differences in STING-dependent and STING-independent intracellular signaling in SAVI²⁷ and CANDLE patients, respectively.^{7, 27} Furthermore, epigenetic remodeling has recently been proposed as mechanism explaining “IFN-sensitization” *in vitro*,^{28, 29} thus the reduction in daily variability in the 25-gene interferon score in baricitinib-treated patients may be consistent with epigenetic remodeling in the context of JAK inhibition, which was recently assessed in a murine model.³⁰ Together, our data confirm the suppressive effect of baricitinib on IFN- α/β receptor signaling *in vivo* and may allow the quantification of residual responses to IFN stimulation in treated patients, which will guide balancing the suppression of the pathologic IFN actions and the maintenance of adequate host responses to infections.

Overall, patients in this compassionate use program have received orally administered baricitinib for over 54 patient-years. Upper respiratory tract infection was one of the most frequently reported TEAEs consistent with the adult rheumatoid arthritis studies.^{31, 32} The unique safety observation in this compassionate use program was BK viremia and BK viruria. One patient was discontinued because BK viremia was found in association with renal disease, but a biopsy to confirm BK nephropathy was not performed. The BK titers in urine have remained stable but had not been tested at baseline, therefore the number of new positive cases could not be assessed. BK virus is ubiquitous and typically acquired in childhood,³³ and long-term natural history data related to BK viruria and viremia are not available. In immunocompetent individuals the infection is asymptomatic despite frequent episodes of viral reactivation and shedding in the urine,^{34–36} but symptomatic reactivation and the development of BK-associated nephropathy has been observed in renal and hematopoietic stem cell transplant populations.³⁷ These data suggest monitoring of viral titers in the blood for this fragile patient population with relatively high baricitinib exposures until more data on the clinical significance become available.

Limitations of this program include the small number of patients with these rare interferonopathies that were assessed, and a large weight and dose range in the enrolled patient population, with no data below a weight of 8.5 kg. Another limitation may be the sparse PK sample collection strategy utilized in the program. However, the repeated assessments conducted in these patients over several months of therapy, the ability to compare results in this patient population to adult data, and the analysis of several biomarkers support the clinical observations of a sustained therapeutic effect of baricitinib on IFN signaling.

This report summarizes the PK of the orally administered drug baricitinib as measured in a mostly pediatric population of patients with severe early-onset interferonopathies, and establishes the effect of this agent on JAK/STAT phosphorylation and more distant markers of IFN signaling, including the 25-gene IFN score and serum IP-10 levels. The proposed oral dosing regimen included in this report represents an initial treatment approach in patients with severe CANDLE, SAVI or other presumed interferonopathies. Given the higher long-term exposure that is required for effective treatment and the likely life-long need for treatment in this patient population, long-term safety and efficacy assessments are needed.

METHODS

Program Approval

The Institutional Review Board (IRB) of the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Institute of Allergy and Infectious Diseases (NIAID) all at the National Institutes of Health (NIH) approved the studies. The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. All parents or legal guardians provided informed consent. Assent was obtained for all patients who were 7 years or older at the time of enrollment or reconsenting.

Patient Population and Program Design

PK data were collected under a compassionate use program for patients with CANDLE, SAVI and CANDLE-related conditions (other interferonopathies) who were unresponsive to standard treatment with conventional or biologic DMARDs (program 14V-MC-JAGA (NCT01724580). Blood samples for pSTAT assessments and gene expression signatures were collected under a natural history study (NCT02974595). Enrolled patients were required to weigh at least 8.5 kg and be at least 17.5 months of age. Key exclusion criteria included active chronic infection such as herpes, hepatitis, HIV, tuberculosis and significant renal disease (eGFR <40 mL/min/1.73 m²).

Patients were initially dosed orally once daily (see Supplementary Methods for details regarding dosage forms). Subsequent dose titrations (defined either as an alteration to the total daily dose or frequency of dosing) were based on clinical symptoms and elevations in systemic inflammatory markers. Patient-specific PK data became increasingly available throughout the program, and were used to monitor safety and efficacy of the drug, and guide further dosing modifications (see Supplementary Methods).

Population Pharmacokinetic Analysis

Sparse PK sampling was performed at least 72 hours after treatment initiation or a dose escalation when steady state attainment was presumed (see Supplementary Methods). If PK samples could not be obtained with the same program visit, they were collected at a subsequent program visit. Blood PK sample collection at the initiation of the program was at 1.5, 8, and 24 hours post-dose and revised to include time 0 (pre-dose), 1, 1.5, and 4 hours post-morning dose, and then prior to and 1.5 hours after the evening dose to account for the shorter half-lives observed in this population. Plasma concentrations were determined using methods as previously described.¹³

Available PK data were analyzed using a popPK modeling approach via a nonlinear mixed-effects modeling in NONMEM (version VII, ICON Development Solutions, Ellicott City, Maryland, USA). One- and two-compartment structural models with first- or zero-order absorption were tested. Intrinsic factors such as age, body weight, body surface area, and renal function expressed by estimated glomerular filtration rate (eGFR) were investigated to assess their influence on CL/F and V/F. Following development of the popPK model, post-

hoc PK parameters were generated for individual patients at program entry (baseline) and the final PK assessment (Supplementary Methods for PopPK modeling).

Pharmacodynamic Marker Analysis

In vitro whole Blood STAT-1 and STAT-3 phosphorylation and baricitinib IC₅₀ determination—A total of 48 blood samples were collected from 8 CANDLE and 4 SAVI patients with the respective blood draws for baricitinib PK analysis (time 0 (pre-dose), 1, 1.5, and 4 hours after the morning dose). Healthy controls who did not receive baricitinib had blood draws at the same time points. Whole blood was stimulated with cytokines IFN- α (PeproTech, Rocky Hill, NJ) for pSTAT-1 assessment, and when possible also IL-6 (Cell Signaling Technology, Danvers, MA) for pSTAT-3 assessment. Median fluorescence intensity (MFI) of pSTAT-1 and pSTAT-3 in CD4+ and CD8+ T cells, B cells and monocytes was measured by flow cytometry as previously described³⁸ and as detailed in the Supplementary Methods. Ratios of stimulated vs. unstimulated MFI values were calculated. IC₅₀ was modeled for pSTAT-1 and pSTAT-3 phosphorylation in all 4 cell types (Supplementary Methods).

Correlations of AUC_{24,SS} with 25-gene IFN score and serum CXCL10/IP-10 levels—Linear mixed model with random slope and intercept with an unstructured variance-covariance matrix were used to assess the effect of drug exposure (AUC_{24,SS}) on biomarkers of IFN signaling (serum IP-10 levels and a standardized 25-gene IFN score (STD25) as described in Supplementary Methods).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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CONFLICT OF INTEREST/DISCLOSURES

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Rare Mendelian interferonopathies are characterized by early-onset chronic systemic and organ-specific inflammation and damage, and are poorly responsive to many conventional and biologic immune-modulating therapies. Janus kinase inhibitors are a novel class of drugs that may have clinical utility in this population.

WHAT QUESTION DID THIS STUDY ADDRESS?

In this compassionate use program, we collected pharmacokinetic (PK) data in primarily pediatric patients treated with the oral JAK1/JAK2 inhibitor, baricitinib. We also assessed the *in vivo* effect of baricitinib on interferon (IFN) biomarkers. These findings supported a proposed oral dosing regimen to aid clinicians managing patients with rare interferonopathies.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

We demonstrate that baricitinib PK is significantly influenced by body weight and renal function in pediatric patients, and provide evidence that baricitinib suppresses IFN signaling *in vivo*. However, overall drug exposures required in this population are higher than those required for the management of rheumatoid arthritis in adults.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This study provides insight into the PK-PD of orally administered baricitinib in patients with rare interferonopathies, and is the first agent in its class to be examined in a primarily pediatric population.

Figure 1. Covariate plots for Relationship between (A) body weight and volume of distribution, V/F and (B) glomerular filtration rate (GFR) on clearance, CL/F

Pt. C1 is an outlier for the V/F (L) estimates (red circle) but not for the clearance (red arrow) (see Supplementary Methods). Scatter plot of covariates versus estimated PK parameters are shown. The solid colored circles represent the individual estimated PK parameters and covariates. Data from the same individual are connected by a solid colored line. The solid black lines represent the relationships between the typical PK parameters and the covariates. The equations for the relationships are: (for A) $V/F = 67.1 \times e^{0.0192 \cdot (WTV - 27.2)}$ and (for B)

$$CL/F = 9.74 \times \left(\frac{eGFR}{146.82} \right)^{0.444}.$$

Cell type	IC ₅₀ (nM)				
	Estimate	Std Error	CV%	95% Confidence Interval	
				Lower Limit	Upper Limit
CD4 T cell	51.1	10.5	20.5%	28.0	74.2
CD8 T cell	43.3	10.9	25.3%	18.9	67.6
CD14 Monocyte	137.7	25.0	18.2%	81.9	193.5
CD19 B cell	189.9	10.8	5.7%	165.8	214.1

Cell type	IC ₅₀ (nM)				
	Estimate	Std Error	CV%	95% Confidence Interval	
				Lower Limit	Upper Limit
CD4 T cell	330.4	121.3	36.7%	56.0	604.7
CD8 T cell	103.2	25.7	24.9%	45.0	161.5
CD14 Monocyte	185.9	66.2	35.6%	36.1	335.7

Figure 2. IC₅₀ values by Cell Type for (A) IFN α -stimulated STAT1 Phosphorylation (pSTAT1), (B) IL-6 stimulated STAT3 Phosphorylation (pSTAT3), and (C) STAT-1 phosphorylation at baricitinib trough levels

(A), (B). Scatter plots of actual data versus model curves for pSTAT by cell type are shown with the median fluorescence intensity (MFI) ratio (stimulated divided by un-stimulated) minus 1 versus the peripheral blood drug level in nM. The solid line and light blue band are the best-fit curve and 95% predictive interval, respectively. The table shows the IC₅₀ (nM) calculated based on this modeling (estimate) with standard error, coefficient of variance, and 95% confidence intervals.

* p -value < 0.01, ** p -value < 0.001, ns: not significant.

Figure 3. Correlation of AUC with (A) 25-gene IFN score and (B) IP-10

Drug exposure ($AUC_{24,SS}$) is significantly negatively correlated with 25-gene IFN score and serum IP-10 levels by F-test for $AUC_{24,SS}$ effect. Each individual is denoted with a different colored line and dots. The heavy red line represents the overall line for the group and the equation is listed below. (A) Correlation of AUC with 25-Gene IFN Score includes 327 observations in 18 patients (all diagnoses). The dashed line represents cutoff of normal 25-gene IFN score based on healthy controls. Equation: $IFN\ STD\ 25 = 431.98 - 0.07220 (AUC_{24,SS})$, slope = -0.096 $p\text{-value for slope} = 0.049$. (B) Correlation of AUC with serum IP-10 levels includes 189 observations in 18 patients (all diagnoses). Equation: $IP-10 = 9060.45 - 2.1432 (AUC_{24,SS})$, slope = -0.197 , $p\text{-value for slope} = 0.0002$.

Table 1

Patient Demographics

Demographics	
Gender	n (%)
Female	6 (33.3)
Male	12 (66.7)
Race	
White	16 (88.9)
Black	2 (11.1)
Ethnicity	
Hispanic or Latino	4 (22.2)
Age (yr)	Mean (min–max)
At protocol enrollment (n= 18)	12.5 (1.2–24.1)
By Diagnosis	Mean (SD)
CANDLE* (n=10)	11.5 (6.9)
SAVI** (n=4)	16.3 (6.7)
CANDLE-like*** (n=4)	12.5 (9.4)

* *PSMB8* (5 homozygous, 1 compound heterozygous), *PSMB4* (compound heterozygous), *PSMB4/PSMB9* (2 digenic), *PSMA3/PSMB8* (1 digenic),

** all *TMEM173*, *N154S* (*de novo*)

*** *SAMHD1* (1 homozygous deletion), unknown (2 patients), one heterozygous *PSMB8* mutation identified

Table 2

Summary of Population Pharmacokinetic Parameter Estimates

Parameter Description	Population Estimate (%SEE)	Intersubject Variability ^A (%SEE)
Absorption duration D1 (hr)	0.971 (14.8%)	---
Apparent Clearance CL/F (L/hr)	9.74 (9.57%)	43.7% (21.5%)
Apparent Volume of Distribution V/F (L)	67.1 (14.2%)	37.3% (90.8%)
Covariate effect of Weight on V/F ^B		
Parameter for WTV-V	0.0192 (15.0%)	---
Covariate effect of GFR on Clearance ^C		
Parameter for GFR-CL	0.444 (24.8%)	---
Residual Error (Proportional, %)	0.486 (7.22%)	

Abbreviations: %SEE = relative standard error of estimation, “---” = fixed to zero, CI = confidence interval, WTV = body weight; GFR = glomerular filtration rate, %CV= coefficient of variation.

^A Reported as %CV, calculated by equation: $100 \cdot \sqrt{e^{\omega} - 1}$, where ω is the standard deviation estimate for the intersubject variability

^B $V/F_{typical} = 67.1 \times e^{0.0192 \cdot (WTV - 27.2)}$

^C $CL/F_{typical} = 9.74 \times \left(\frac{eGFR}{146.82} \right)^{0.444}$

Table 3

Summary of Predicted PK Parameters by Renal Function and Body at Final PK Visit (Exclude Subject C1)

eGFR Categories	120 mL/min/1.73 m ²		
Weight Categories	<20kg (n=2)	20–40kg (n=5)	>40kg (n=3)
		2	C4
		C3	C5
Subject	C8	S1	C9
	O2	S3	C10
		S4	S2
			O1
			O3
			O4
Patient Characteristics ^A			
Age (years)	10.0 (3.2 – 16.8)	9.9 (9.0 – 19.1)	21.2 (18.8 – 25.5)
Weight (kg)	15.2 (13.9 – 16.6)	30.9 (27.2 – 37.1)	59.2 (46.1 – 97.2)
BSA (m ²)	0.63 (0.58 – 0.67)	1.09 (0.95 – 1.10)	1.65 (1.42 – 2.08)
eGFR (mL/min/1.73 m ²)	214 (196 – 233)	165 (148 – 189)	132 (122 – 154)
TDD/Weight (mg/kg)	0.53 (0.48 – 0.58)	0.22 (0.16 – 0.33)	0.14 (0.11 – 0.26)
			0.40 (0.37 – 0.42)
			0.18 (0.13 – 0.23)
PK Parameters ^B			
AUC _{0–24,ss} (nM*h)	2580 (12.6%)	2020 (20.2%)	1940 (39.0%)
AUC _{0–24,ss} /Dose ^C (nM*h/mg)	322 (12.6%)	292 (36.6%)	193 (22.2%)
C _{max} (nM)	171 (7.6%)	150 (15.8%)	136 (32.2%)
t _{1/2} (h)	4.4 (30.3%)	5.0 (44.0%)	7.0 (37.4%)
V/F (L)	53.1 (17.3%)	66.2 (25.5%)	141.0 (28.0%)
CL/F (L/hr)	8.4 (12.6%)	9.2 (36.6%)	13.9 (22.2%)
			5.3 (4.7%)
			9.2 (82.7%)

Abbreviations: eGFR: estimated glomerular filtration rate; BSA: body surface area; TDD: total daily dose; PK: pharmacokinetics; AUC_{0–24,ss}: area-under-the-concentration-time curve over 24 hours at steady-state; C_{max}: maximum concentration; t_{1/2}: half-life; V/F: apparent volume of distribution; CL/F: apparent clearance; CV: coefficient of variation; C refers to patients with CANDL, S to patients with SAV1 and O to patients with other interferonopathies, O4 is the patient with the SAMHD1 deletion who was retrospectively diagnosed with Aicardi Goutieres syndrome (AGS) 5.

^A median (minimum–maximum)

^B geometric mean (%CV)

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$C_{AUC24,SS}/Dose = AUC_{24,SS}/total\ daily\ dose$
 D using data from V214 (~1 year prior to final PK visit)
 E using data from V212.1 (~1 week prior to final PK visit)

Table 4

Suggested Dosing Table Based on Weight and Renal Function (eGFR)

Weight Class	Morning Dose	Afternoon Dose	Evening Dose	Total Daily Dose	Duration Min/Max Dose (mg/kg)	Dosing Frequency
eGFR 120 mL/min/1.73 m²						
Initial Dose						
<20 kg	2 mg	2 mg	2 mg	6 mg	0.3/NA	TID
20–40 kg	3 mg	—	3 mg	6 mg	0.15/0.3	BID
>40 kg	4 mg	—	4 mg	8 mg	NA/0.2	BID
First Dose Escalation						
<20 kg	2 mg	2 mg	2 mg	8 mg	0.4/ NA	QID
20–40 kg	3 mg	2 mg	3 mg	8 mg	0.2/0.4	TID
>40 kg	5 mg	—	5 mg	10 mg	NA/ 0.25	BID
Second Dose Escalation (only in patients > 40 kg)						
>40 kg	6 mg	—	6 mg	12 mg	NA/0.3	BID
with eGFR <120 mL/min/1.73 m²						
Initial Dose^A						
<20 kg	2 mg	—	2 mg	4 mg	0.2/NA	BID
20–40 kg	2 mg	—	2 mg	4 mg	0.1/0.2	BID
>40 kg	2 mg	—	2 mg	4 mg	NA/0.1	BID
First Dose Escalation (only for patients with eGFR 60 mL/min/1.73 m²)						
<20 kg	2 mg	2 mg	2 mg	6 mg	0.3/NA	TID
20–40 kg	3 mg	—	3 mg	6 mg	0.15/0.3	BID
>40 kg	3 mg	—	3 mg	6 mg	NA/0.15	BID

Abbreviations: eGFR: estimated glomerular filtration rate

^A Baricitinib should not be used in patients with eGFR <30 mL/min/1.73 m².