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Pediatric Extrapolation Approach for U.S. Food and Drug Administration Approval of Brexpiprazole in Patients Aged 13 to 17 Years with Schizophrenia

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Abstract

A pharmacokinetic (PK) bridging approach was successfully employed to support the dosing regimen and approval of brexpiprazole in pediatric patients aged 13-17 years with schizophrenia. Brexpiprazole was approved in 2015 for the treatment of schizophrenia and the adjunctive treatment of major depressive disorder in adults based on efficacy and safety data from clinical trials. On January 13, 2020, the US Food and Drug Administration issued a general advice letter to sponsors highlighting the acceptance of efficacy extrapolation of certain atypical antipsychotics from adult patients to pediatric patients considering the similarity in disease and exposure–response relationships. Brexpiprazole is the first atypical antipsychotic approved in pediatrics using this approach. The PK data available from pediatric patients aged 13-17 years have shown high variability due to the limited number of PK evaluable subjects, which limits a robust estimation of differences between adult and pediatric patients. The PK model-based approach was thus utilized to evaluate the appropriateness of the dosing regimen by comparing PK exposures in pediatric patients aged 13-17 years with exposures achieved in adults at the approved doses. In addition to exposure matching, safety data from a long-term open-label clinical study in pediatric patients informed the safety profile in pediatric patients. This report illustrates the potential of leveraging previously collected efficacy, safety, and PK data in adult patients to make a regulatory decision in pediatric patients for the indication of schizophrenia.

Keywords

antipsychotics, brexpiprazole, exposure–response, pediatric extrapolation, pharmacokinetic

Introduction

Brexpiprazole was approved by the US Food and Drug Administration (FDA) in 2015 for the treatment of schizophrenia and the adjunctive treatment of major depressive disorder in adults. As an atypical antipsychotic, brexpiprazole has a partial agonist activity at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors. The absolute oral bioavailability of brexpiprazole is about 95%. After single or multiple once-daily dose administrations, brexpiprazole exposure (C_{max} and AUC) increased the dose proportionally. Clearance is mainly through metabolism with major involvement of cytochrome P450 (CYP) 3A4 and CYP2D6. The estimated terminal elimination half-life of brexpiprazole is about 91 h.[1]

Brexpiprazole has recently been approved for the treatment of schizophrenia in pediatric patients (13 to 17 years old).[1] Effectiveness of brexpiprazole in pediatric patients was extrapolated from adult data, based on the comparable systemic exposure of brexpiprazole in pediatric and adult patients within the therapeutic dose range, and the safety profiles in pediatric patients obtained from a long-term open-label clinical study were deemed acceptable. In addition to observed pharmacokinetic (PK) data, population PK analysis indicated the systemic exposure (C_{max} and AUC) of brexpiprazole in pediatric patients aged 13-17 years was comparable to that in adult patients across the dose range from 0.5 mg to 4 mg.

Historically, one or more adequate and well-controlled clinical studies in pediatric patients have been required to support approval for the treatment of schizophrenia in pediatric patients. As a result, pediatric labeling information can be significantly delayed for novel atypical antipsychotics, even for those

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already approved for use in adults, like brexpiprazole. In the interim, healthcare providers rely on limited evidence-based literature to make important therapeutic decisions, often resulting in the off-label use of antipsychotics in pediatric patients.[2] The number of pediatric studies evaluating atypical antipsychotics has increased over the last decade, and the majority of pediatric studies intended to evaluate treatments for schizophrenia have demonstrated favorable benefit–risk profiles that ultimately led to approval. To expedite the availability of empirically supported prescribing information for atypical antipsychotics for the treatment of schizophrenia and bipolar I disorder in pediatric patients, based on these findings and on extrapolation methods by which prior data obtained in adults may inform future drug development in the pediatric population,[3–7] the FDA issued a general advice letter to sponsors in 2020 communicating the acceptance of an efficacy extrapolation approach for atypical antipsychotic drugs for pediatric patients 13 years of age and older. This determination was based on the similarity of disease characteristics, the similarity of symptomatic changes observed in acute schizophrenia clinical trials in pediatric patients and adults receiving placebos, and on an analysis of multiple antipsychotic drugs, conducted by the FDA, that demonstrated a similar exposure–response relationship in pediatric and adult patients with schizophrenia.[4–6] For drugs that share a similar mechanism of action (D2-receptor antagonism or partial agonism, 5-HT1A partial agonism, and/or 5-HT2A antagonism) to currently FDA-approved antipsychotics for the treatment of schizophrenia and/or bipolar disorder, the following three requirements should be satisfied for this extrapolation approach to be considered appropriate to support application of a pediatric indication: (i) An approved indication in adults; (ii) a PK analysis to determine a dosing regimen that provides similar drug exposures (at doses demonstrated to be effective in adults) in pediatric and adult patients; and (iii) a long-term open label safety study(ies) in pediatric patients.

Because available data and regulatory experience mainly exist with antipsychotics whose pharmacological effects are thought to be mediated through D_2 receptor antagonism or partial agonism, 5-HT_{1A} receptor partial agonism, and/or 5-HT_{2A} receptor antagonism, currently the extrapolation approach is only considered for those antipsychotics. For drugs with a different mechanism of action, clinical trial(s) to evaluate effectiveness in pediatric patients are still required for a pediatric indication. There is the potential for more informed use/greater utilization of the extrapolation approach in pediatric drug development as knowledge and experience accumulate in different psychiatric conditions in pediatric and adult populations.[5,7–9]

Brexpiprazole is the first atypical antipsychotic approved for the treatment of schizophrenia in a pediatric population based on an efficacy extrapolation approach. This report aims to explain the basis for this approval, with a focus on the PK bridging approach.

Methods

Data

The PK data from three clinical trials in adults (studies 1, 2, and 3) and two clinical trials in pediatric subjects (study 4 in children aged 6 to 12 years old and study 5 in pediatric patients aged 13 to 17 years) were used to develop a population PK model of brexpiprazole (Table 1). The Applicant asserts that the study protocols were approved by the Institutional Review Board or Independent Ethics Committee at each respective trial center.[10] Consistent with ethical principles for the protection of human research subjects, no trial procedures were performed on trial candidates until written consent or assent had been obtained from them and/or their legally acceptable representative.

Population PK Analysis

A population PK model was developed and submitted to the FDA by the Applicant. The details of the applicant's PK model are available elsewhere.[10] Briefly, the PK of brexpiprazole was best described by a two-compartment model with sequential zero-first-order absorption and linear elimination. The PK model had clearance and volume of distribution allometrically scaled by body weight (raised to the power of 0.75 for clearance, and 1 for volume of distribution). The PK model was refined by estimating weight scaling factors for clearance and volume of distribution from the available data. The PK modeling was performed using NONMEM® version 7.4.3 (ICON development solutions). Noncompartment analysis (NCA) metrics and data visualization were conducted in R (R version 4.1.2, https://www.r-project.org/).

Determination of Pediatric Dosing Based on the Clinical Trial Experience

The refined population PK model was used to simulate exposure to brexpiprazole in adults and pediatric patients aged 13-17 years based on the dosage listed in Table 2. Briefly, the demographic information was taken from the available PK dataset (studies 1-3, and 5) of brexpiprazole using random sampling with replacement approach. The PK profiles of 50 subjects per dose group were simulated ($n = 20$ times per subject) to create 1000 PK profiles for each age group. Outcomes of interest for each individual, AUC, C_{max}, and C_{trough} were then derived from the simulated PK profiles and compared across different age groups.

Table 1. Brief Summary of Clinical Trials Included in the Pharmacokinetic Modeling Dataset

Study No.	Title	Dose Range (mg)	Age Range (#subjects)
1	A Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Tolerability, Safety, and Pharmacokinetics of Ascending Single Oral Doses of OPC-34712 in Healthy Subjects (arm 1)	0.2 to 4	Adults (n = 38)
2	A Phase 1, Multi-center, Randomized, Double-blind, Comparator-Controlled Study to Assess the Tolerability, Safety, Efficacy, and Pharmacokinetics of Ascending Multiple Oral Doses of OPC-34712 in Adult Subjects with a Diagnosis of Schizophrenia or Schizoaffective Disorder	1 to 4	Adults (n = 24)
3	A Phase 1, Open-Label, Multiple-Dose, Parallel-Group Study to Assess the Pharmacokinetics and Safety of Oral OPC-34712 in Healthy Subjects	0.5 to 3	Adults (n = 42)
4	A Phase 1, Single-Dose, Sequential Cohort, Nonrandomized Crossover Trial to Assess the Pharmacokinetics, Safety, and Tolerability of Oral Brexpiprazole in Children (6 to <13 Years old) with Central Nervous System Disorders	0.75 to 3	6 to 9 years old (n = 12); 10 to 12 years old (n = 12)
5	A Phase 1, Multicenter, Open-Label, Dose Escalation Trial to Assess the Safety, Tolerability and Pharmacokinetics of Oral Brexpiprazole (OPC-34712) in Adolescents with Schizophrenia or Other Related Psychiatric Disorders	0.5 to 4	13 to 17 years old (n = 43)

Table 2. Titration Schedule Used for Pharmacokinetic Simulations in Adults and Pediatric Patients Aged 13-17 Years

Treatment Day	Adult	Pediatric Patients Aged 13 to 17 Years
Day 1 to 4	1 mg/day	0.5 mg/day
Day 5 to 7	2 mg/day	1 mg/day
Day 8 (and onward)	4 mg/day	2 mg/day (weekly dose increases were made in 1-mg increments. The maximum recommended daily dosage is 4 mg.)

Safety of Brexpiprazole in Pediatric Patients 13 to 17 Years Old

The safety of brexpiprazole was assessed in pediatric patients aged 13-17 years old with schizophrenia enrolled in a multicenter, single-arm, 24-month study, who were treated with open-label brexpiprazole 1, 2, 3, or 4 mg dose daily. Safety assessments included adverse event collection, laboratory measures, and vital signs. The data were examined for important safety concerns associated with the use of brexpiprazole in adults as well as novel safety signals.

Results

Data

A summary of the five clinical trials used in the PK modeling analysis is presented in Table 1. The final analysis included a total of 3674 evaluable brexpiprazole concentrations from 161 subjects with 61% of subjects being adults. The median(range) age of adult and pediatric populations was 30 (18,53) years and 13 (6,17) years, respectively. The median(range) weight of adult and pediatric populations was 81 (59, 121) kg and 58 (20,115) kg, respectively.

Population PK Analysis

The Applicant's population PK model with standard allometric scaling appears to overpredict the PK profiles of brexpiprazole in the pediatric population aged 6-17 years and an alternative PK model was utilized by the FDA. The Applicant's PK model was refined by estimating weight scaling factors (θ_{WT}) for clearance and volume of distribution from the available data using Equation (1).

$$\theta_i = TV_\theta * \left(\frac{WT_i}{70}\right)^{\theta_{WT}}$$

where θ_i is the value of the parameter for the i_{th} individual, TV_θ represents the typical value of the PK parameter for an individual weighing 70 kg, WT_i is the weight of the individual, and θ_{WT} is the effect of weight on the PK parameter.

The PK parameters of the refined PK model are shown in Table 2. Specifically, the standard weight scaling factors for clearance (i.e., 0.75 for both clearance and intercompartmental clearance) and volume of distribution (i.e., 1 for both central as well as peripheral volume of distribution) were replaced with the model-estimated coefficients, that is, 0.207 and 0.77, respectively. The remaining PK parameters estimated from the refined PK model were similar to the Applicant's PK model. Overall, the PK parameters were estimated with reasonable precision (Table 3). The refined population PK model fits the data adequately in both adult and pediatric subjects aged 6-17 years.

Dosing Determination for Pediatric Patients Aged 13 to 17 Years Using PK Matching Approach

The PK profiles and parameters of brexpiprazole in adult and pediatric subjects aged 13-17 years were

Table 3. Population Pharmacokinetic Parameter Estimates of Brexpiprazole

Parameter	Definition	Estimate (RSE%)
Fixed Effect		
D1 (mg/h)	Rate of dose into oral absorption compartment	0.925 (5%)
Ka (1/h)	Oral first-order absorption rate constant	1.47 (6%)
CL (L/h)	Apparent clearance for subjects who are not poor or ultra-rapid CYP2D6 metabolizers	1.33 (4%)
Vc (L)	Apparent central volume of distribution	77.6 (3%)
Q (L/h)	Inter-compartmental clearance	0.831 (13%)
Vp (L)	Volume of distribution in peripheral compartment	28.4 (6%)
CL_weight	Effect of weight on CL and Q: power for (CL or Q/70)	0.207 (56%)
V_weight	Effect of weight on Vc and Vp: power for (Vc or Vp/70)	0.77 (10%)
Random Effect: Inter-Individual Variability CV % (RSE %)		
IIV_D1	IIV on D1	58.4% (6%)
IIV_Ka	IIV on Ka	70.0% (6%)
IIV_CL	IIV on CL	53.1% (7%)
IIV_Vc	IIV on Vc	31.6% (7%)
IIV_Vp	IIV on Vp	48.4% (17%)
Residual Variability Estimate (RSE %)		
Error 1	Proportional residual error	0.034 (12%)
Error 2	Additive residual error	0.004 (191%)

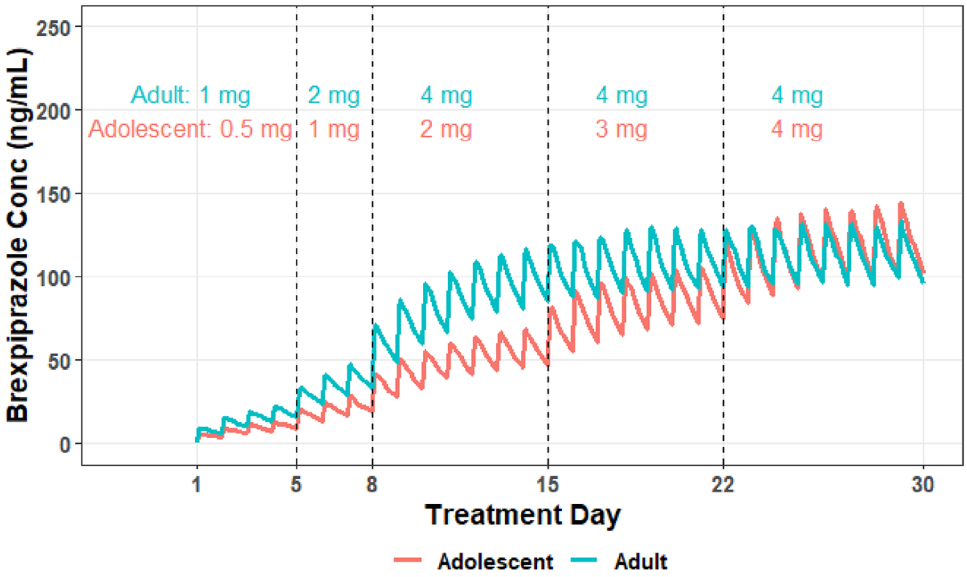

Figure 1. Median simulated pharmacokinetic profiles for adults and pediatric patients aged 13-17 years following the recommended titration schedules.

simulated based on the dosage listed in Table 2. Specifically, for pediatric subjects aged 13-17 years, a lower starting dose (i.e., 0.5 mg/day in pediatrics vs. 1 mg/day in adults) and slower titration (weekly dose increment of 1 mg) were proposed by the Applicant. Thus, it takes longer for adolescents to reach the maximum 4-mg dose. Of note, study 5 has tested both 0.5 and 1 mg as starting doses and employed a slower but more frequent titration schedule, that is, 0.5 mg/day increment every 2 days to reach the target cohort doses (1, 2, 3, or 4 mg/day). A comparison of the simulated median PK profiles between adults and pediatric subjects aged 13-17 years is presented in Figure 1. During the titration phase, the brexpiprazole concentrations in pediatric subjects aged 13-17 are lower as compared to adults, primarily due to the lower starting dose and smaller titration increments. The recommended target dose is 2 to 4 mg once daily for both adults and pediatrics. Once the maintenance phase is reached, the steady-state PK profiles of brexpiprazole in pediatric patients aged 13-17 years are comparable to those in adults at the same target dose (Figure 1).

In addition to the PK profile comparison, the PK parameters of adult and pediatric groups were also

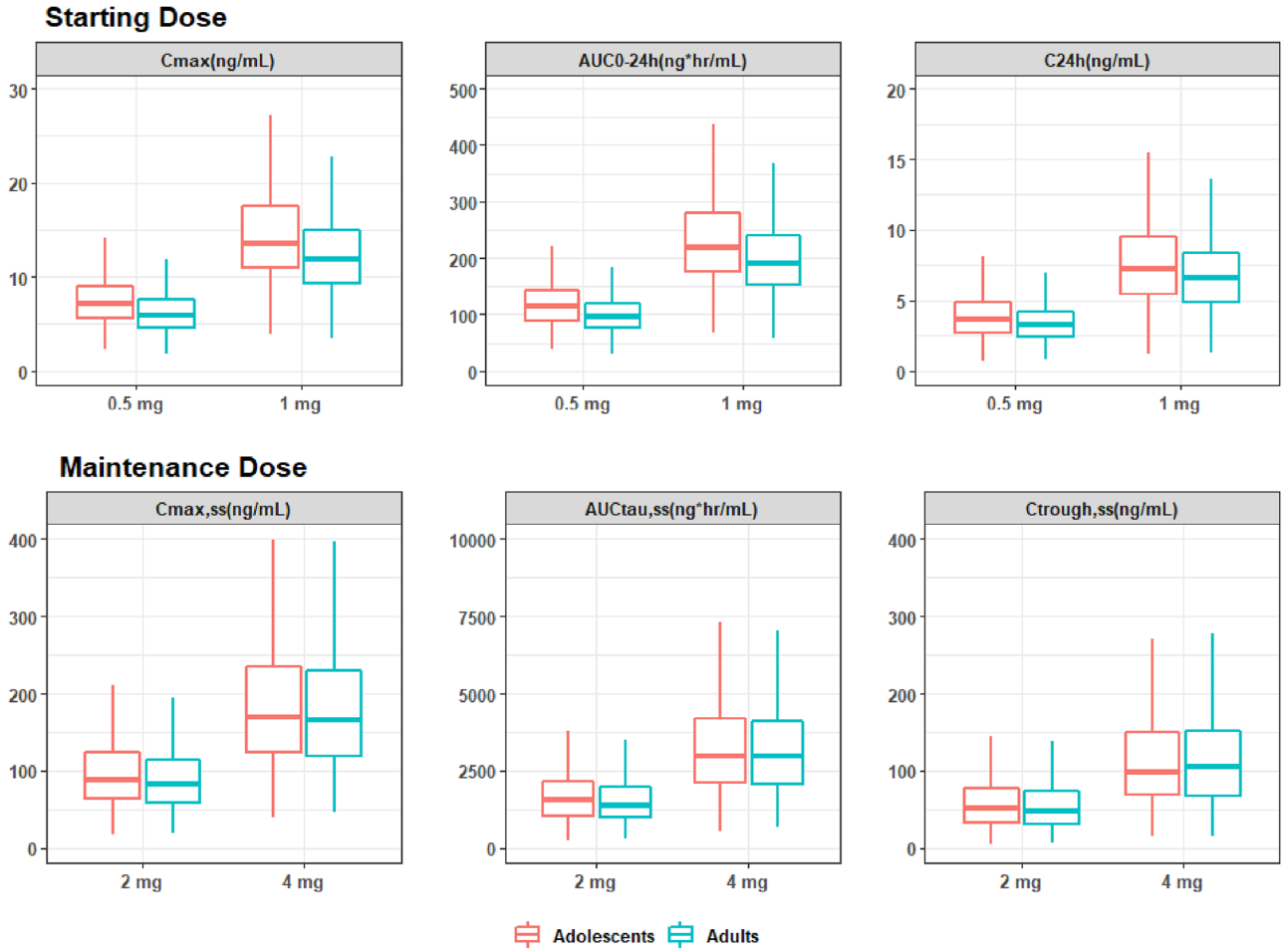

Figure 2. Pharmacokinetic exposure following single starting doses of brexpiprazole 0.5 and 1 mg (upper panel) and steady-state pharmacokinetic exposure following daily doses of brexpiprazole 2 and 4 mg (lower panel) for adults and pediatric patients 13-17 years old. Box represents the interquartile range (IQR); solid line is the median; Upper and lower whiskers represent 1.5 times the IQR.

compared at various doses. Figure 2 shows a comparison of predicted PK exposure ($AUC_{0\text{-}24h}$, C_{max}, C_{24h}) following a single dose of brexpiprazole 0.5 and 1 mg, as well as predicted steady-state PK exposures ($AUC_{tau,\,ss}$, $C_{max,\,ss}$, $C_{trough,\,ss}$) following daily doses of brexpiprazole 2 and 4 mg between pediatric patients aged 13-17 years and adults. As expected, single-dose PK exposure in pediatric patients aged 13-17 years at the proposed starting dose (0.5 mg) is 40% lower when compared with PK exposure in adults at the proposed starting dose (1 mg). Steady-state PK exposure in pediatric patients aged 13-17 years at 2 and 4 mg are comparable (within 10% difference) with PK exposure in adults at the same dose level.

Additionally, the impact of weight on the PK of brexpiprazole was also evaluated to assess the necessity for weight-based dosing, taking into account the body weight of patients enrolled in the aforementioned clinical trials. The PK exposure following a single dose of brexpiprazole 0.5 and 1 mg ($AUC_{0\text{-}24hr}$, C_{max}, C_{24hr}) and following daily doses of brexpiprazole 2 and 4 mg ($AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$) for pediatrics is stratified by body-weight quantiles and compared with those for adults (Figure 3). At the same dose level, the PK exposure (C_{max}, AUC, and C_{trough}) obtained in adults and pediatrics of different weight bands is comparable, and thus weight-based dosing is not warranted.

The open-label safety data revealed minor differences between adults and pediatric patients in the incidence of adverse reactions and laboratory abnormalities but were generally consistent with the safety experience in adults and supported the extrapolation approach and the recommended dosing.[1] However, a high incidence of abnormal prolactin values in the data requires further evaluation in the post-market setting. To address uncertainties about the incidence of abnormal prolactin values, additional controlled safety data are required to be submitted to the US FDA as a post-marketing requirement.

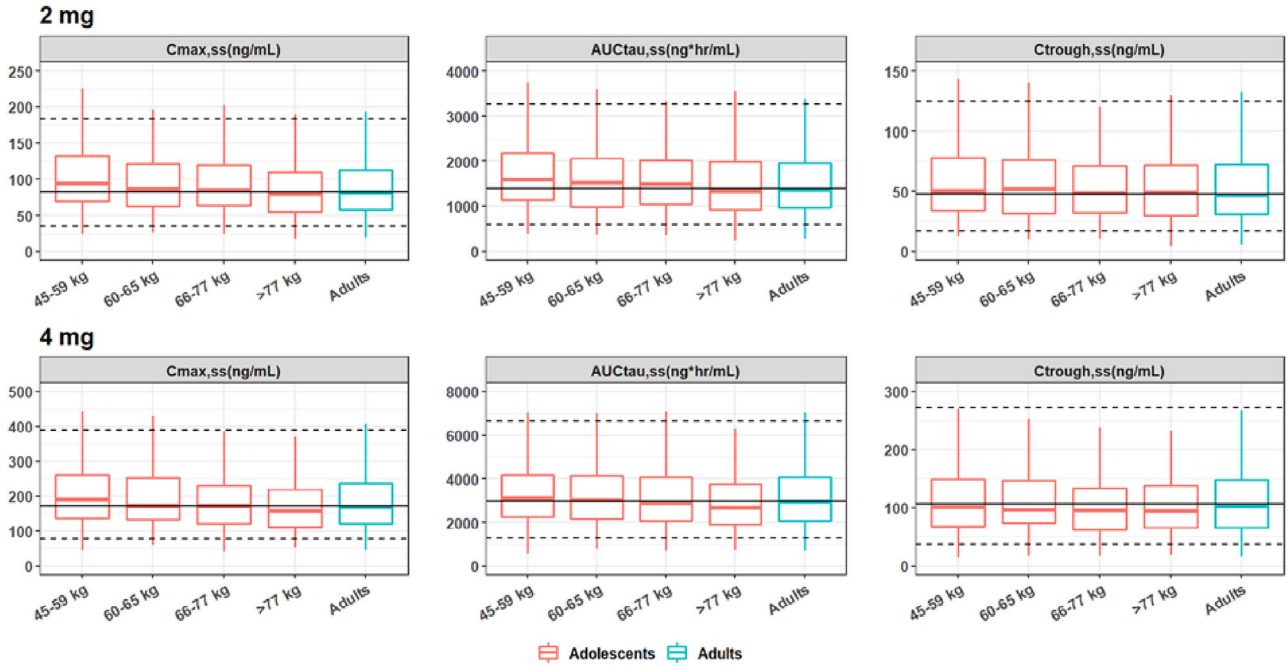

Figure 3. Comparison of simulated steady-state pharmacokinetic exposures following daily doses of brexpiprazole 2 mg (top row) and 4 mg (bottom row) for adults and four weight groups in pediatrics. The black lines represent the median (solid line), 5th percentile (dash line), and 95th percentile (dash line) of simulated exposure metrics in adults. Box represents the interquartile range (IQR); solid line is the median; upper and lower whiskers represent 1.5 times the IQR.

Discussion

A PK matching approach was successfully employed to determine a dosing regimen and support approval of brexpiprazole in pediatric patients aged 13-17 years with schizophrenia. The PK data available from pediatric patients aged 13-17 years have shown high variability due to the limited number of PK evaluable subjects, which limits a robust estimation of differences between adult and pediatric patients. The PK model-based approach was thus utilized to determine dosage in pediatric patients aged 13-17 years by matching PK exposures in pediatric patients to a range of exposures achieved in adults at the approved doses. A lower brexpiprazole starting dose of 0.5 mg/day and slower titration were recommended in pediatric subjects aged 13-17 years as decreased exposure may yield a better tolerability profile in these patients. In addition, studies from adult patients suggest that the full antipsychotic effect of brexpiprazole may not be evident for a few weeks even after steady-state exposures have been reached. Therefore, overall, the proposed titration scheme in adolescent patients seems appropriate.

The recommended and maximum doses are similar in both adult and pediatric groups as similar doses provide similar drug exposures in adult and pediatric patients. At steady state, based on simulation results, PK exposure metrics (AUC_{tau}, C_{max}, C_{trough}) following daily doses of brexpiprazole (2 and 4 mg) seem comparable between adults and adolescents (Figure 2). Therefore, similar pharmacological effects are expected between these two patient populations. Weight-based dosing is also not warranted for this pediatric age group due to similar exposures across different weight bands. The PK simulation results were consistent with the Applicant's analysis regardless of the choice of the final population PK model (i.e., similar simulation results were obtained from the original[10] and refined models). The dose recommendations for the target population (i.e., adolescent subjects aged 13 to 17 years) were the same based on either of these PK models. Overall, these results supported the extrapolation of efficacy for brexpiprazole from adults to pediatric patients aged 13-17 years.

Extrapolation can be considered when a disease's progression and response to the interventions in the adult and pediatric populations are similar. The US FDA has determined that it is acceptable to extrapolate the effectiveness of atypical antipsychotic drugs approved for the treatment of schizophrenia in adults to pediatric patients 13 years of age and older. This determination was based on the similarity of disease characteristics, the similarity of symptomatic changes observed in acute schizophrenia clinical trials in pediatric patients and adults receiving a placebo, and on an analysis of multiple antipsychotic drugs, conducted by the FDA, that demonstrated a

similar exposure–response relationship in pediatric and adult patients with schizophrenia.[4–6] Briefly, a recent analysis[4] has assessed and confirmed the similarity in disease pathophysiology, dose–exposure relationships, and exposure–response relationships between adult and pediatric patients with schizophrenia. The analysis evaluated data collected from nine adult programs (clinical trials: n = 30; number of subjects n = 10,644) and seven pediatric programs (clinical trials, n = 7; number of subjects n = 2122; age range: 12 to 17 years old). The time course of the placebo responses (mean change from baseline in total Positive and Negative Syndrome Scale [PANSS] score in subjects taking placebo) was found to be almost identical in pediatric and adult patients experiencing an acute exacerbation of schizophrenia. At the same dose level, steady-state exposures in the two populations were generally overlapping. Additionally, placebo-corrected change from baseline in total PANSS score at week 6 was also found to be similar across the range of exposures. The same conclusions were quantitatively substantiated by an empirical disease–drug–trial model analysis.[6] These findings provided the basis to extrapolate the efficacy of brexpiprazole from adults to pediatric patients aged 13-17 years for the treatment of schizophrenia. Of note, the efficacy extrapolation approach is not applicable for pediatric subjects aged less than 13 years, considering the rare onset of schizophrenia in this younger age group.[11]

A recent example of utilizing a PK bridging and efficacy extrapolation approach is the approval of topiramate as initial monotherapy in pediatric patients aged 2-9 years with epilepsy.[12] This extrapolation approach is now fully accepted in the development of drugs for the treatment of partial-onset seizures (POS).[13] The efficacy of drugs approved for the treatment of POS in adults can be extrapolated to pediatric patients 1 month of age and above. Other examples utilizing this PK bridging approach for determining pediatric dosing include levofloxacin for the treatment of postexposure inhalation anthrax[14] and piperacillin/tazobactam for the treatment of several types of infections.[15]

The benefits of the extrapolation approach in extending adult efficacy findings to the pediatric population, when used appropriately, include lowering the cost of pediatric drug development, accelerating access to medication, and reducing off-label use in the pediatric patient population. Utilization of the extrapolation approach has been increasingly employed recently in pediatric drug development. A more than twofold increase in the use of a complete efficacy extrapolation approach has been reported for the pediatric studies submitted to the FDA in recent years: Among the 166 drug products submitted between 1998 and 2008, about 14.5% of them (n = 24) have used a complete extrapolation approach[7]; and among the 157 drug products submitted between 2009 and 2014, 34% of them (n = 53) employed that approach.[8] There is still a knowledge gap for many indications/drug classes that limits pediatric extrapolation of efficacy. The scientific community should continue to leverage available human and nonclinical data to better understand the pathophysiology of the disease to minimize uncertainties in pediatric extrapolation assumptions.[8] The modeling and simulation approaches can play an important role in enhancing the application of pediatric extrapolation of efficacy.

Conclusion

This serves as the first example of an atypical antipsychotic approved for the treatment of schizophrenia in a pediatric population based on an extrapolation of efficacy and using a PK bridging approach to establish an efficacious dosing regimen. There is the potential for more informed use/greater utilization of the extrapolation approach in pediatric drug development as knowledge and experience accumulate in different psychiatric conditions in pediatric and adult populations.

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Author Contributions

All authors contributed to the writing and editing of this manuscript.

Conflicts of Interest

The authors declared no competing interests for this work.

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Data Availability Statement

The data that support the findings of this study are not available due to legal restrictions.

Disclaimer

This article reflects the views of the author and should not be construed to represent FDA's views or policies. Huixia Zhang and Luning Zhuang participated in this work while employed at the FDA, but their current affiliation has changed. Huixia Zhang is an employee of AstraZeneca US and Luning Zhuang is an employee of Bristol Myers Squibb.

Their participation in this work does not represent the views or endorsement of their current employers.

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