Brexpiprazole: First approval of a pediatric efficacy application of an atypical antipsychotic for schizophrenia relying on extrapolation of adult effectiveness

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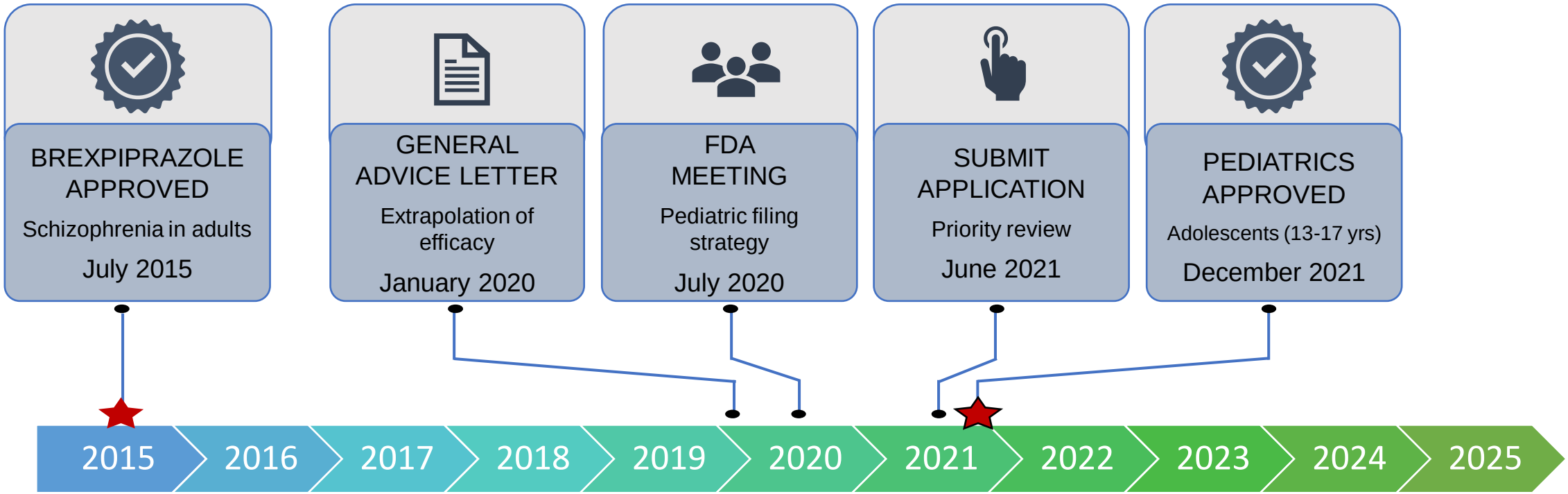
Disclosures

- Full-time employee of Otsuka Pharmaceutical Development & Commercialization, Inc.

Challenges of CNS trials in pediatrics

- Randomized, placebo-controlled trials (PCT) still widely used in many CNS indications
  - Currently considered the gold standard in most indications
  - Allow comparison of drug vs placebo with objective interpretation of data, minimize bias
  - Homogenous population may limit generalizability to the general population
- Recruitment challenges and ethical considerations
  - Limitations on PCTs in some countries; some investigators will not conduct PCTs in pediatrics
  - Low subject completion rate for RCTs in some pediatric CNS indications
  - Concerns about impact on long term outcomes due to time off treatment
  - Specific risks associated with some indications, e.g., increase in suicidal behaviors in adolescent schizophrenia
- Long duration of trials can lead to cohort effects and increases the likelihood of a non-informative trial
- Time delays occur in approvals for pediatric drugs due to lengthy trials relating to challenges in recruitment
  - Off label usage can occur where there are delays in approval, with a lack of safety data to support use in the pediatric population

Brexpiprazole for treatment of schizophrenia in adolescents was FDA-approved 3 years earlier by use of extrapolation of adult efficacy data



*study completion date

FDA General Advice Letter:
All requirements met for schizophrenia indication

Requirements to support indication relying on extrapolation	Available
• FDA approved for treatment of schizophrenia in adults	☑
• Similar mechanism of action	☑
• PK analysis to determine dosing regimen	☑
• Long-term open label safety study(ies) in pediatrics	☑

FDA meeting to align on population PK analyses and safety data package

Population PK model and simulations used to predict systemic exposure in adolescents based on PK matching with adult data

Pop PK model developed from 5 phase 1 trials:

2 pediatric trials

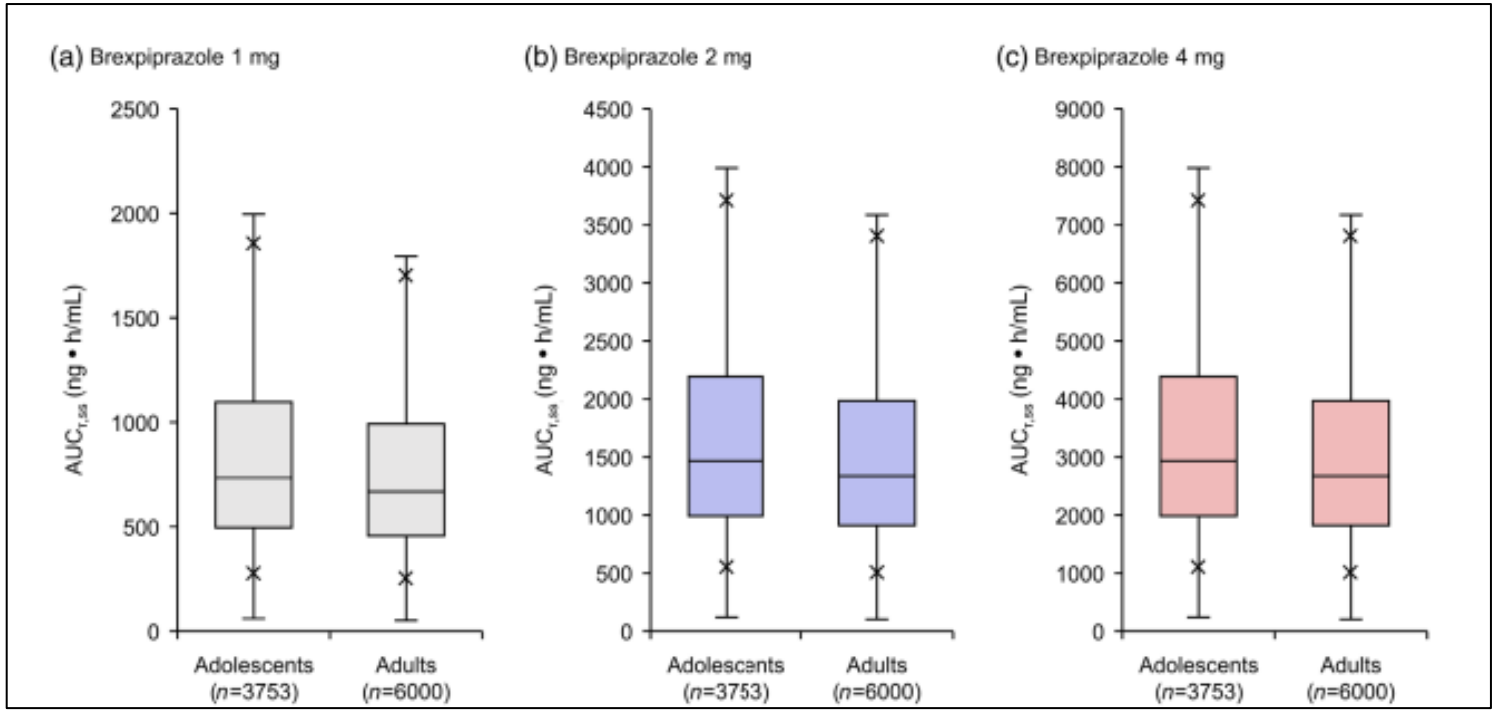
+

3 adult trials

Objective:

- Describe brexpiprazole PK in adults, adolescents and children
- Use model to perform simulations to inform dose selection in adolescents with schizophrenia

Simulated $AUC_{T,SS}$ in adults and adolescents aged 13 – 17 years with schizophrenia following once-daily administration of brexpiprazole dosed at (a) 1 mg, (b) 2 mg, and (c) 4 mg.



Wang, Y., Wang, X., Larsen, F., Cahill, D., Zoubroulis, A., Ward, C., Kohegyi, E. and Raoufinia, A. (2023), Population Pharmacokinetic Analysis of Brexpiprazole to Support its Indication and Dose Selection in Adolescents With Schizophrenia. J Clin Pharm, 63: 1290-1299. https://doi.org/10.1002/jcph.2307

Open-label safety study in adolescents demonstrated brexpiprazole treatment of schizophrenia has a similar safety profile as observed in adults

Extent of Exposure to Brexpiprazole During the 24-month Open-label Treatment Period in Adolescent Schizophrenia Patients		
Days of exposure to brexpiprazole	# patients at time of submission	# patients at Day120 safety update
≥ 90 days (3 months)	130	161
≥ 180 days (6 months)	103	140
≥ 540 days (18 months)	36	53
≥ 630 days (21 months)	25	42
Any exposure	167	194

Overall Safety Conclusion:
The reported events from pediatric clinical trials are consistent with those known to occur with brexpiprazole in the adult population and do not indicate any increased risk for adolescents with schizophrenia who are treated with brexpiprazole[1].

[1] REXULTI (brexpiprazole) US Prescribing Information. Rockville, MD: Otsuka America Pharmaceutical, Inc.; Dec 2021

Additional Considerations

Labeling

- On-going, open-label long-term safety data available at time of submission

Global Acceptance

- Other Health Authorities request controlled-efficacy data for pediatric approvals

On-going Trial Results

- What happens if controlled-efficacy trial does not meet primary endpoint?

Controlled efficacy clinical data confirms brexpiprazole efficacy in adolescents with schizophrenia

- Submission to Agency in progress
- Clinical data will be presented at future congresses

CLINICAL STUDY REPORT

A Multicenter, Randomized, Double-blind, Placebo- and Active-controlled Trial to Evaluate the Efficacy of Brexpiprazole Monotherapy for the Treatment in Adolescents (13-17 years old) With Schizophrenia

Protocol No. 331-10-234

- Treatment with brexpiprazole 2 to 4 mg/day showed statistically significant improvement compared to placebo for the primary efficacy endpoint, change from baseline to Week 6 in the PANSS Total Score [NCT03198078]