Fenfluramine is being developed as adjunctive therapy for the treatment of seizures associated with Dravet syndrome, a rare and severe epileptic encephalopathy. Fenfluramine was previously marketed as an appetite suppressant for the treatment of adult obesity but was withdrawn from worldwide markets when its use, often in combination with phentermine, was associated with cardiovascular adverse events, including cardiac valvulopathy and primary pulmonary hypertension. The most recent published pharmacokinetic (PK) data for fenfluramine are 6-120 mg/day, although there are reports in the literature of higher doses being used. In adults, the risk of cardiac valvulopathy was 9-fold higher in patients taking 60 mg/day or more compared with patients taking 40 mg/day. This study was performed to estimate the exposure to fenfluramine in children at doses between 0.2 and 0.8 mg/kg/day with a maximum dose of 30 mg/day.

Monte Carlo Simulation

Monte Carlo simulation was performed to estimate the fenfluramine exposure likely to be observed in children with Dravet syndrome receiving fenfluramine at doses of 0.2-0.8 mg/kg/day with a maximum dose of 30 mg/day.

Key assumptions:
- ZK008 contains racemic fenfluramine with equal parts d- and l- Fenfluramine
- More robust PK data are available for d-fenfluramine, so total fenfluramine clearance was based on the assumption that d-fenfluramine exposure in children and adults is oral bioavailability (F) is 69%.

METHODS

The most recent published pharmacokinetic (PK) data for fenfluramine or d-fenfluramine in adults was used to provide an estimate of the clearance for fenfluramine following oral administration. Inadequate information regarding the timing of blood collection relative to time of dosing made quantitative comparison of these data to the adult data unreliable.

RESULTS

• A dataset of 2000 simulated children aged 2-18 years was generated assuming a mean of 40 L/h with a CV% of 33%.

• Only the outlier values from predictions in children overlap the mean reported values in adults from the literature.

CONCLUSIONS

• Prediction of steady-state fenfluramine exposure in a simulated population of 2000 children with age-appropriate weights was enabled by applying allometric scaling to adult CLT estimates for fenfluramine.

• The expected fenfluramine exposure from the proposed ZX008 dosing regimen (0.2-0.8 mg/kg/day; maximum 30 mg/day) is predicted to be significantly lower than that of adults treated with the originally approved fenfluramine product at labeled doses of 60-120 mg/day.

REFERENCES

1. Zyco LLC et al. (2020) APM paper. 2020. 3.7.4 prepared fenfluramine.