**Introduction**

Influenza morbidity and mortality in children are highest in the aged 0–<1 year. Reports of drug exposures on which to base oseltamivir dosing in this high-risk population have led to conflicting recommendations in the USA and Europe.

As part of the effort to address these issues, two studies focusing on the pharmacokinetics (PK), pharmacodynamics (PD) and safety of oseltamivir in this age group have recently been carried out.

The National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) supported two studies focusing on the pharmacokinetics and safety of oseltamivir in young children: the Collaborative Antiviral Study Group (CASG) study and the European study WP22849.

**Methods**

**Patients**

- **Patients** had influenza symptoms for ≤6 hours and a positive PCR or rapid diagnostic test at the time of study entry.

- **Age-stratified weight-based doses of oseltamivir and suspension twice daily** for 5 days were used in both studies (Table 2).

**Population pharmacokinetic analysis and covariate model development**

Non-linear mixed effects modelling (NLMEM) was used, with patient weight stratified by a linear two-compartment model with first-order absorption and the oseltamivir carboxylic (OC) metabolite absorbed post-dose. Model compartments, model parameters and covars for DC conversion were assumed, and the DC central compartment volume was obtained.

- **Weight** was used to account for body size differences across age groups. Clearance and volume parameters were non-linearly scaled using fixed exponents of 0.7 and 1, respectively. Covariates included age, sex, post-conceptual age, gestational age, bodyweight, gender and ethnicity were investigated using the full model approach.

- The final model was evaluated using visual and posterior predictive checks and a non-parametric bootstrap. Predictive targets were extracted either (a) in simulated PK analyses or (b) in a bridging analysis. In the latter, infant exposure measures were compared to exposure measures based on historical data for older children and adults receiving approved and clinically tested doses.

**Integrated pharmacokinetic/ pharmacodynamic analysis**

- **Exposure-based PK/PD analyses included:** temperature reduction versus time, time to resolution of fever, treatment emergent adverse events, and relationships between drug exposure and safety/toxicity.

**Pharmaceutical bridging analysis**

- **Pediatric dose exposure targets in the bridging analysis** were based on the area under the curve (AUC) and a previously published study in young children (age 0–<1 year) where oseltamivir 30mg twice daily data for 5 days showed the lowest probability of a sustained virological response:
  - Targets were steady-state AUC, >2,400 mg•h/L in infants, ≥1,500 mg•h/L in children, 1,200 mg•h/L in children (absolute proportion above average 73%, 69% and 68%, respectively).
  - The lowest DC exposure were required to be similar to those with approved dosing regimens in parallel populations, with adequate safety/toxicity margins for AUC and maximum concentration (Cmax).

- **Concentration data** for bridging inclusion were exposed data from children aged 1–2 or 3–5 years and steady-state data from adults receiving 75mg to exceed oseltamivir twice daily.

**Model validation**

- **Modelling of the new exposure-response studies** showed the PK/PD analysis showed a drug-exposure parameter (AUC; modelled) vs. viral load (real-time) relationship.

**Results**

**Patients**

- **Patients** had influenza symptoms for ≤6 hours and a positive PCR or rapid diagnostic test at the time of study entry.

- **Age-stratified weight-based doses of oseltamivir and suspension twice daily** for 5 days were used in both studies (Table 2).

**Population pharmacokinetic model**

- The concentration courses of oseltamivir and OC in infants aged ≤<1 year were accurately described by the three-compartment PK model with inhalation absorption. In the model, two compartments are attributed for the first compartment of DC.

- For a typical infant weighing 8.4kg and aged 24 weeks:
  - oseltamivir PK parameters were estimated as: oral clearance (CL): 67L/hr (95% CI 45.8–95.5); volume of distribution (Vd): 11.6L (95% CI 10.4–12.9); and the absorption half-time (t1/2) for the DC compartment was 24 hours.

- DC PK parameters were estimated as: oral clearance (CL): 0.88L/hr (95% CI 0.60–1.3); and the absorption half-time (t1/2) for the DC compartment was 24 hours.

**Population pharmacokinetic model**

- DC PK parameters were estimated as: oral clearance (CL): 0.88L/hr (95% CI 0.60–1.3); and the absorption half-time (t1/2) for the DC compartment was 24 hours.

**Conclusion**

- The disposition of oseltamivir and OC in children aged ≤1 year described by a PK model extrapolating adult oral dosing is linear and a strong increase of DC clearance with age.

- **Age-stratified** groups, 3mg/kg twice daily oral oseltamivir and OC exposures known to be safe and well tolerated, with the potential to optimise the role of antiviral, subsequent resistance or treatment failure.

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**Figure 1.** Model diagnostics. (a) Goodness-of-fit to the final model; DC. (b) Visual predictive check: concentration versus time after dosing by age group.

**Figure 2.** Model simulations and PK bridging. Comparisons of predicted distributions of steady-state exposures at 3mg/kg in healthy adults and pediatric patients. (a) AUC; (b) Cmax; (c) Cmin.