Population Pharmacokinetic Modeling of an Investigational Novel Once-Daily (QD) Lithium Carbonate Extended Release (XR) Bi-Layer Matrix Formulation Tablet to Support Formulation Switching and Pediatric Dosing

MSR57

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Introduction

- Lithium carbonate is a first-line maintenance therapy for bipolar I disorder, with demonstrated efficacy in relapse prevention and suicide risk reduction[1]
- Due to its narrow therapeutic index, therapeutic drug monitoring is required to maintain plasma concentrations within the recommended range of 0.6-1.2 mmol/L 10-14 hours post dose[2-4]
- Currently approved lithium formulations include two-times-daily (BID) extended-release (ER) and three-times-daily (TID) immediate-release (IR)[4,5]
- The maximum dosages are 1800 mg/day for adult and pediatric patients weighing more than 30 kg, and 1500 mg/day for pediatric patients weighing 20 to 30 kg[6]
- This novel QD lithium carbonate XR formulation is designed with bi-layer matrix technology consisting of a gastroretentive placebo layer and a controlled-release active layer[7]
- This new formulation may reduce intra-day peaks and troughs and provide consistent plasma levels, potentially improving tolerability, while maintaining bioequivalence to existing therapies[4,7]
- A population pharmacokinetic (popPK) model of lithium carbonate was developed to simulate PK profiles of this novel QD lithium carbonate XR formulation in adult and pediatric patients[7]

Study Objectives

- Characterize QD lithium carbonate XR pharmacokinetics, including evaluation of formulation-switching strategies from BID ER and TID IR formulations
- Assess dosing strategies in pediatric and adolescent patients aged 7 to <18 years using fixed allometric scaling

Methods

- Data were pooled from three Phase 1 crossover studies conducted in 80 healthy adult volunteers. Studies included single-dose evaluations of QD lithium carbonate XR 900 mg given under fed and fasted conditions; steady-state evaluations of QD XR 900 mg under fed conditions only; and QD XR 600 mg, BID ER 450 mg, and TID IR 300 mg under fed conditions only
- A nonlinear mixed-effects popPK model was developed using a two-compartment disposition structure with linear clearance. Absorption was best described using two transit compartments with first-order absorption and inter-occasion variability on the transit rate constant (K_{tr})
- Covariates evaluated included body weight (implemented via fixed allometric scaling) in apparent clearance and volumes of distribution, formulation (IR, ER, XR) on relative bioavailability (FREL) and K_{tr}, food status (fed, fasting) on FREL and K_{tr}, and circadian rhythm effects on K_{tr}
- Model selection was guided by Bayesian Information Criterion (BIC), goodness-of-fit diagnostics, precision of parameter estimates, and stratified visual predictive checks (VPCs)
- Each simulation was performed with 2000 virtual subjects using the final model under fed conditions. Simulations evaluated steady-state exposure and formulation-switching scenarios across QD lithium carbonate XR (600–1800 mg daily), BID ER 450 mg (900 mg daily) and QD ER 450 mg, and IR regimens including TID 300 mg (900 mg daily) and BID 300 mg (600 mg daily), as shown in the figures. Additional dose levels and switching scenarios were evaluated in the full simulation dataset but are not displayed here
- All analyses were performed using Julia/Pumas (version 2.6.1) on the JuliaHub computing platform (version 6.8.0)

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Results

PK Modeling

- The final model described lithium concentration–time profiles across all formulations and fed and fasting conditions (fasting for QD XR only). Transit absorption modeling significantly improved fit relative to first-order absorption models
- Estimated apparent clearance (CL) was 8.26 L/hr. Transit rate constants differed by formulation: lithium carbonate XR (0.365 h^{-1}), ER (0.801 h^{-1}), and IR (2.247 h^{-1}), reflecting progressively slower absorption with extended-release formulations
- Food significantly affected both the rate (K_{tr}) and extent (relative bioavailability) of absorption. Including circadian rhythm effects improved model fit by capturing delayed absorption following evening doses

Adult Simulations

(Figure 1, Table 1)

- Simulations of 2000 virtual adults demonstrated dose-proportional increases in exposure across 600-1800 mg daily dosing

Formulation-Switching Simulations

(Figure 2)

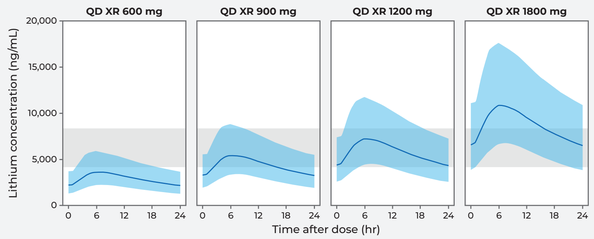
- Switching simulations evaluated transitions from BID ER and TID IR regimens to equivalent total daily doses of QD XR (except ER 450 mg daily to XR 600 mg daily)
- Results demonstrated minimal changes in AUC, C_{max}, and C_{min} after switching at steady state. Exposure differences were not predicted to be clinically meaningful
- These findings support direct conversion to QD lithium carbonate XR at equivalent total daily doses without requiring complex titration strategies

Pediatric Simulations

(Figure 3)

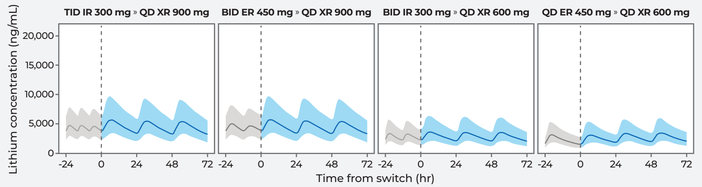
- Allometric scaling enabled extrapolation to 2000 virtual children (7 to <12 years) and 2000 virtual adolescents (12 to <18 years)
- Simulations predicted higher exposure in younger and lower-weight patients at equivalent doses. Patients weighing 20 to <30 kg were predicted to exceed the upper therapeutic trough range at doses ≥1200-1500 mg daily

Figure 1: Projected steady-state profiles of QD lithium carbonate XR (linear scale).



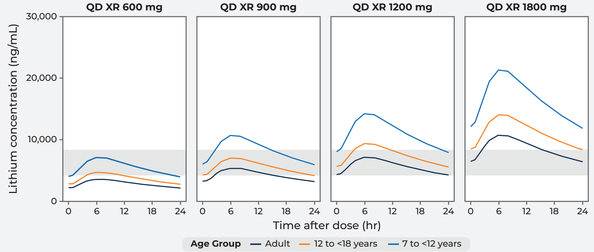
- Model-projected steady-state lithium concentration–time profiles for QD XR (600-1800 mg daily) demonstrated dose-proportional increases in systemic exposure across the therapeutic dose range
- Median (solid line) and 5th-95th percentile prediction intervals (blue shaded region) show expected variability, while the grey shaded band represents the target therapeutic trough range (0.6-1.2 mmol/L), illustrating the proportion of patients predicted to achieve therapeutic trough concentrations at each dose

Figure 2: Projected exposure of QD lithium carbonate XR after switching from IR or ER formulations.



- Model-projected lithium concentration–time profiles were generated following a switch from IR or ER formulations to QD XR at dose-equivalent regimens (600-1800 mg daily). These profiles illustrate systemic exposure before and after the switch (dashed line = time of switch)
- Median (solid line) and 5th-95th percentile prediction intervals (shaded region) demonstrate that switching maintains overall systemic exposure while producing smoother, less-fluctuating concentration profiles consistent with once-daily dosing
- Full analysis (up to 1800 mg daily) showed dose-proportional exposure and consistent switch profiles; only 600 mg and 900 mg daily regimens are shown here

Figure 3: Projected steady-state median PK profiles of QD lithium carbonate XR by age group (adults, adolescents, and children).



- Model-projected steady-state median lithium concentration–time profiles were generated for QD lithium carbonate XR at doses of 600-1800 mg daily and were stratified by age group (adults, adolescents 12 to <18 years, and children 7 to <12 years). The profiles demonstrate differences in systemic exposure across age groups
- At equivalent doses, predicted exposures are higher in younger age groups, with children showing the greatest concentrations and adolescents intermediate relative to adults
- The grey shaded band represents the therapeutic trough range (0.6-1.2 mmol/L); simulations suggest that higher doses (eg, 1800 mg daily) may result in trough concentrations exceeding the upper limit in some adolescents and children
- An 1800 mg daily dose is not supported for pediatric patients weighing <30 kg. These results align with current FDA weight-based maximum dosing recommendations

Table 1: Summary statistics of projected QD lithium carbonate XR exposures at steady state in adults.

PK Parameter (unit)		600 mg daily	900 mg daily	1200 mg daily	1800 mg daily
AUC_{0-24} (ng/mL*h)	Median	70227	105341	140454	210681
	Mean (SD)	73559 (22256)	110339 (33384)	147119 (44512)	220678 (66769)
C_{max} (ng/mL)	Median	3760	5639	7519	11279
	Mean (SD)	3952 (1260)	5928 (1890)	7903 (2520)	11855 (3780)
C_{min} (ng/mL)	Median	2177	3265	4353	6530
	Mean (SD)	2287 (766)	3431 (1150)	4575 (1533)	6862 (2299)

- Median steady-state AUC0–24 increased approximately in a dose-proportional manner across the 600 to 1800 mg daily range
- Median trough concentrations (Cmin) remained within or near the therapeutic range for most adults at approved doses, with limited predicted exceedance at 1800 mg daily

Conclusions

- A popPK model adequately described lithium concentration–time profiles across novel once-daily lithium carbonate XR 600 mg and 900 mg and reference IR/ER formulations. This model is suitable to predict XR lithium concentrations across the range of approved doses and in both adults and pediatric patients with a weight as low as 20 kg
- Simulations demonstrated dose-proportional increases in steady-state exposure with QD XR dosing across the approved adult dose range
- Switching from BID ER or TID IR to the novel QD XR formulation at equivalent total daily doses was predicted to result in minimal changes in AUC, C_{max}, and C_{min} at steady state, with exposures remaining within the expected therapeutic range
- Pediatric simulations incorporating fixed allometric scaling supported current weight-based dosing recommendations, while predicting higher trough concentrations at higher approved doses in children and adolescents weighing 20 to <30 kg
- Overall, the popPK model supports QD lithium carbonate XR dosing in adults and pediatric patients and predicts negligible changes in systemic exposure when switching from currently available IR or ER formulations at steady state

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Disclosures

Bates JA, Phull R, Gaudana R, and Yarasani R are current employees of Almatica Pharma LLC. Gobburu J is a current employee of the University of Maryland School of Pharmacy and is a co-founder of Vivpro Corporation and Pumas-AI Inc. Tagen M and Kumar PRM are current employees of PumasAI Inc. Korth-Bradley J is a current employee of Vivpro Corporation and consultant for Alvogen (Almatica).