Background: TBAJ-876 is a second-generation diarylquinoline. NC-009, a phase II dose-finding study, is underway. Rapid delivery of individual $AUC_{0\text{-}24h}$ values from sparse PK samples at Days 15 and 56 is desired at the time of top-line analysis after 8 weeks of treatment. Trapezoidal integration may be inaccurate, because during a profile, samples are collected only pre-dose and 1, 3, and 5 hours post-dose. Bayes estimates from a PopPK model would require the time-consuming construction of an analysis dataset. Several recent studies have demonstrated that machine learning (ML) models can accurately predict the AUC from sparse samples (1-7). We compare the accuracy and precision of trapezoidal integration versus ML to predict $AUC_{0\text{-}24h}$ using sparse data collected according to the design of NC-009.

Methods: All simulations were performed in Simulx (Lixoft) using a PopPK model developed from phase I studies. For each virtual patient, we simulated: 1) Reference $AUC_{0\text{-}24h}$ values for Days 15 and 56 by integrating the model without residual variability. 2) Drug concentrations with residual variability according to the sampling schedule in NC-009. Besides the sparse profiles at Days 15 and 56, this included weekly trough samples, which were used as additional inputs to the ML models. The simulated drug concentrations were used to predict $AUC_{0\text{-}24h}$ for Days 15 and 56 using both trapezoidal integration and ML. All simulations were performed under three scenarios to account for noncompliance: 100% compliance, 85% compliance, and 70% compliance. The sample size for each compliance scenario was 1500 virtual patients. For trapezoidal integration, we used the linear-up-log-down method. For ML, we used the Xgboost algorithm from the tidymodels library in R. We developed two ML models. For ML model 1, the data was split into training and test data sets which are balanced when it comes to compliance. For ML model 2, the data was split into training and test data sets which are not balanced when it comes to compliance. This is to assess the trained model on test data with different compliance assumptions than the training data. To assess the accuracy and precision of predictions, we calculated the relative mean prediction error (rMPE) and the relative mean absolute prediction error (rMAPE), respectively.

Results

For trapezoidal integration, the rMPE and rMAPE for predicting the $AUC_{0\text{-}24h}$ for Day 15 were 2.4% and 13.2%, respectively, and for Day 56 they were 5.3% and 12.4%, respectively. For the ML model 1, they were 0.3% and 6.8%, respectively, on Day 15 and 0.42% and 6%, respectively, on Day 56. For ML model 2, they were 0.8% and 7.1%, respectively, on Day 15 and 0.5% and 6.5%, respectively, on Day 56 (Table 1).

Discussion

The ML AUC predictions were more accurate and precise, with lower rMPE and rMAPE, compared to the trapezoidal method. The ML model performed well even when assumptions of compliance for the test data set were different compared to the training data set. ML prediction can be used as an input for exposure response analysis during drug development.

Table 1. rMPE and rMAPE for AUC predictions using trapezoidal integration and ML

AUC	**rMPE %**	**rMAPE %**
Trapezoidal integration, $AUC_{0\text{-}24}$ prediction for Day 15 trapezoidal integration	2.4	13.2
Trapezoidal integration, $AUC_{0\text{-}24}$ prediction for Day 56	5.3	12.4
ML model 1, $AUC_{0\text{-}24}$ prediction for Day 15	0.3	6.8
ML model 1, $AUC_{0\text{-}24}$ prediction for Day 56 ML	0.42	6
ML model 2, $AUC_{0\text{-}24}$ prediction for Day 15	0.8	7.1
ML model 2, $AUC_{0\text{-}24}$ prediction for Day 56 ML	0.5	6.5