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Enclosure:

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Evaluation of Tolvaptan Effect in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Using Inverse Probability of Censoring Weighting for Long-term Extension Data

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INTRODUCTION

- In long-term extension (LTE) clinical trials switching treatment arms is common amongst placebo participants. Inverse Probability of Censoring Weighting [1,2,3] (IPCW) was invented to recreate balanced treatment arms by assigning weights to patients without switching.
- Another possible issue during LTE is that no comparators exist, leading to bias in comparisons between treatments [4].
- In this research, we aim to create a control group for treatment comparison and determine whether IPCW can decrease bias raised from crossover in long-term data by using data from TEMPO 3:4 trial and its LTE TEMPO 4:4.

OBJECTIVE

Using data from TEMPO 3:4 trial and its LTE TEMPO 4:4, we created a control group for placebo patients, calculated weights by using IPCW, and conducted a series of analyses:

1) estimate time to end stage kidney disease (ESKD) by using Cox regression models. These models used time associated variance-covariance matrix to decrease errors and IPCW to handle the errors due to unbalanced treatment arms;
2) estimate average decline in eGFR between placebo and tolvaptan by using mixed-effects models.

METHODS

- Created a control group for placebo patients (n=180) who did not roll over to LTE in order to have comparators in LTE by using 478 Placebo patients at baseline from TEMPO 3:4:
  - Matched in a 1:1 ratio by sex, age, eGFR, and TKV.
  - Matching criteria: sex +/-0, age+/-0.5, eGFR+/-5 and TKV +/-250.
- Applied IPCW to calculate the stabilized weights using logistic regression models with baseline variables age, sex, race, and a time-varying variable, TKV.
- Stabilized weights estimated for each individual for each time interval (t), using the formula below [5]:

$$\widehat{W}(t) = \prod_{k=0}^{t} \frac{Pr\left[C(k) = 0 | \overline{C}(k-1) = 0, \overline{A}(k-1), V, T > k\right]}{Pr\left[C(k) = 0 | \overline{C}(k-1) = 0, \overline{A}(k-1), \overline{L}(k), T > k\right]}$$

METHODS (continued)

where (a) the numerator represents the probability of an individual remaining uncensored at the end of interval k given that he or she was uncensored at the end of the previous interval (k − 1), conditional on baseline characteristics and treatment history.

(b) The denominator represents that same probability but differs from the numerator because it is conditional on baseline characteristics, treatment history, and time-dependent characteristics.

Statistical methods:

- Time to ESKD with matched LTE in Cox regression models
  - time-varying covariates with IPCW (model 1)
  - ignore the crossover and analyze as ITT (model 2)
  - time-varying covariates (model 3)
- Estimate average decline on eGFR between placebo and Tolvaptan in mixed models
  - with matched LTE, use IPCW, intercept, time, and crossover or not as random effects (model 4)
  - excluding the placebo data at the time of switching (model 5)
  - ignore the crossover and analyze as ITT (model 6)

RESULTS

Table 1. Hazard Ratios for time to ESKD with matched LTE.

Model	Treatment	Hazard Ratio (95% CI)
Model 1 (IPCW)	Tolvaptan	0.17 (0.05, 0.54)
Model 2 (ITT)	Tolvaptan	0.38 (0.20, 0.75)
Model 3 (Time-varying)	Tolvaptan	0.22 (0.09, 0.56)

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DISCLOSURES

Huan Jiang and Zhen Zhang are employees of Otsuka Pharmaceutical Development & Commercialization, Inc.

RESULTS (continued)

Table 2: Average declines on eGFR between placebo and tolvaptan.

Model	Treatment	n	Slope/year (95% CI)
Method 4(IPCW)	Tolvaptan	920	-2.93 (-3.95, -1.91)
	Placebo	478	-4.22 (-5.62, -2.83)
Method 5 (No Placebo in LTE)	Tolvaptan	920	-3.27 (-3.42, -3.11)
	Placebo	478	-3.66 (-3.96, -3.37)
Method 6 (ITT)	Tolvaptan	920	-3.26 (-3.42, -3.11)
	Placebo	478	-4.28 (-4.51, -4.05)

SUMMARIES

- The estimated HR was lower in IPCW model than HRs from ITT and the time-varying Cox models in Table 1, which means that the IPCW performed well in reducing errors from unbalanced treatments arms.
- In mixed models, for tolvaptan patients, the estimated slope in IPCW model was the smallest one. The estimated slope for placebo patients in IPCW model was between the estimators in ITT method and no placebo model. The reason might be the limited data used to match for the missing treatment arms.

CONCLUSIONS

- By using the IPCW method, we found that being in the tolvaptan treatment, ADPKD patients had an 83% lower likelihood to develop ESKD with an annual decrease rate of 2.93 mL/min/1.73 m^2, compared to these who were in placebo treatment during TEMPO 3:4 trial and its LTE.

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