Figure S5

Trial: TEMPO 3:4  Patient: 5

Last Dose Day: 372

Day from First Dose Date

ALP
ALT
AST
BILI
Trial: TEMPO 3:4  Patient: 6

Last Dose Day: 245

Figure S6

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials AJKD, Page 6 of 51"
Figure S8

Trial: TEMPO 3:4  Patient: 8

Last Dose Day: 432

-100 0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400

Day from First Dose Date

0 1 2 3 4 5 6 7 8 9 10

xULN

ALP  ALT  AST  BILI
Figure S17

Last Dose Day: 201

Trial: TEMPO 3:4   Patient: 17

ALP
ALT
AST
BILI

Day from First Dose Date

Trial: TEMPO 3:4   Patient: 17

Last Dose Day: 201

ALP
ALT
AST
BILI

Day from First Dose Date
Figure S19

Trial: TEMPO 4:4  Patient: 2

Last Dose Day: 94

Day from First Dose Date

xULN

ALP  ALT  AST  BILI

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 19 of 51
Figure S23

Trial: TEMPO 4:4  Patient: 6

Last Dose Day: 128

Day from First Dose Date

NLTN

ALP
ALT
AST
BILI
Figure S24

Trial: TEMPO 4:4  Patient: 7

Last Dose Day: 182

Trial: TEMPO 4:4   Patient: 7

ALP
ALT
AST
BILI

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 24 of 51
Figure S28

Trial: REPRISE  Patient: 2

Last Dose Day: 133

Day from First Dose Date

Trial: REPRISE  Patient: 2

Last Dose Day: 133

Day from First Dose Date

ALP
ALT
AST
BILI

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 28 of 51
Figure S29

Trial: REPRISE  Patient: 3

Last Dose Day: 136

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 29 of 51
Figure S31

Trial: REPRISE  Patient: 5

Last Dose Day: 302

Alpers et al, “Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials” AJKD, Page 31 of 51
Figure S32

Trial: REPRISE   Patient: 6

Last Dose Day: 229

Trial: REPRISE   Patient: 6

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials AJKD, Page 32 of 51
Figure S33

Trial: REPRISE   Patient: 7

Last Dose Day: 344

Day from First Dose Date

ALT

AST

BILI

ALP

Trial: REPRISE   Patient: 7

Last Dose Day: 344
Figure S34

Trial: REPRISE  Patient: 8

Last Dose Day: 402

-100 0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400

Day from First Dose Date

ALP
ALT
AST
BILI

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 34 of 51
Figure S35

Trial: REPRISE    Patient: 9

Last Dose Day: 129

Day from First Dose Date
Figure S37

Trial: REPRISE  Patient: 11

Last Dose Day: 109

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 37 of 51
Figure S38

Trial: REPRISE   Patient: 12

Last Dose Day: 169

Alpers et al, "Clinical Pattern of Tolvaptan-Associated Liver Injury in Trial Participants With ADPKD: An Analysis of Pivotal Clinical Trials" AJKD, Page 38 of 51
Trial: REPRISE   Patient: 13

Last Dose Day: 352

Figure S39
**Figure S43.** Liver chemistries over time plots of patients with ADPKD who were rechallenged after an initial ALT elevation due to tolvaptan-induced liver injury

**S43A:** Positive rechallenge after an initial ALT >3x ULN; upon rechallenge ALT elevation was ≤3x ULN but at least double the baseline ALT; patient recovered to normal or near normal ALT levels off tolvaptan

This is the most common type of rechallenge in which the drug is discontinued and the episode resolves completely before rechallenge is attempted. The same pattern is repeated with each subsequent episode in response to decreasing doses, showing the absence of a dose relationship. Note that the initial episode showed the highest peak elevations of ALT and AST, it took about 2 months to resolve, and each subsequent episode had a lower enzyme peak.
**S43B**: Positive rechallenge after an initial ALT ≤3x ULN but at least double the baseline ALT; upon rechallenge ALT elevation was >3x ULN, patient recovered to normal or near normal ALT levels off tolvaptan

Rechallenge in which the drug is discontinued and the episode resolves completely before rechallenge is attempted. The subsequent readministration of tolvaptan (at a reduced dose) shows a higher elevation in a shorter period of time compared to the initial elevation.
**S43C:** Positive rechallenge after an initial ALT >3x ULN; upon rechallenge, ALT elevation was ≤3x ULN but at least double the baseline ALT; patient recovered to normal or near normal ALT levels on tolvaptan

This rechallenge is common in that the drug was discontinued upon an initial ALT peak; however, upon rechallenge at the same total daily dose of 120 mg, the second increase in ALT took around 7 months, which is longer than what is typical. Also, after the second rechallenge at a lower total daily dose of 90 mg, the patient was able to remain on tolvaptan for the rest of the trial, with ALT reaching normal or near normal levels.
**S43D:** Negative rechallenge after an initial ALT >3x ULN; upon rechallenge ALT elevation was normal or near normal levels

An initial ALT elevation of >3x ULN was followed by a dechallenge that resulted in an ALT returning to normal or near normal levels. Upon rechallenge at a reduced total daily dose of 90 mg, ALT remained at normal to near normal levels, allowing the patient to remain on tolvaptan for the remainder of the trial.
S43E: Adaptation after an initial ALT >3x ULN, upon the last rechallenge, the drug was not discontinued, even during ALT elevations, and while remaining on drug, ALT returned to normal or near normal levels.

**Trial: TEMPO 3:4**  
**Adjudication Result: Probable**

The first episode of enzyme elevation led to a decrease in total daily dose of 30 mg from 120 to 90 mg, with resolution of the episode and continuation of that dose. However, that adaptation was short lived, and the drug was discontinued when the second elevation occurred. Tolvaptan was restarted at 60 mg, lower than either of the two previous doses, and a third elevation was noted, but the dose was continued (with periodic brief lapses) and the elevation resolved, although it took longer than the prior two episodes. At 60 mg the enzymes fell to normal or near normal levels and remained there. This case demonstrates both dose-related effects as well as adaptation, and it is not possible to distinguish the relative importance of each factor.

ADPKD, autosomal dominant polycystic kidney disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.
Item S1: Description of clinical trials included in the analysis

The TEMPO Clinical Program

Trial design and eligibility criteria for TEMPO 3:4 and TEMPO 4:4 have been described. In brief, subjects who enrolled in TEMPO 3:4 had image-confirmed diagnosis of ADPKD, total kidney volume ≥750 mL, and an estimated creatinine clearance rate ≥60 mL/min. Of the 1445 subjects enrolled (tolvaptan, 961; placebo, 484), 1441 had at least one post-baseline assessment of hepatic injury. Tolvaptan was administered twice daily, starting at a morning/afternoon dose of 45/15 mg and titrated to 60/30 mg and 90/30 mg based on tolerability, with down-titration allowable at any time to as low as the starting dose (45/15 mg). Subjects were treated for 36 months or until early discontinuation. In TEMPO 4:4, 871 subjects from TEMPO 3:4 (tolvaptan, 557; placebo, 314), received open-label tolvaptan at their highest tolerated dose for a minimum of 24 additional months.

The REPRISE Clinical Program

Trial design and eligibility criteria for REPRISE and the long-term extension have been described. REPRISE randomized 1370 ADPKD subjects (tolvaptan, 683; placebo, 687) who were either 18 to 55 years of age with an estimated glomerular filtration rate (eGFR) of 25 to 65 mL/min/1.73 m² or 56 to 65 years with an estimated GFR of 25 to 44 mL/min/1.73 m² and historical evidence of a decline in the estimated GFR of more than 2.0 mL/min/1.73 m² per year. Whereas eligibility criteria for TEMPO 3:4 targeted a trial population with primarily early-stage ADPKD (>80% stage 1 or 2 CKD), REPRISE enrolled an older population with mainly later-stage ADPKD (5% stage 2, 75% stage 3, and 20% stage 4 CKD). In REPRISE, an 8-week pre-randomization period included sequential placebo and tolvaptan run-in phases, during which each subject’s ability to take tolvaptan at morning/afternoon doses of 60 mg/30 mg or 90 mg/30 mg without dose-limiting side effects was assessed. Subsequently, 1370 subjects were randomly assigned in a 1:1 ratio to receive tolvaptan or placebo for 12 months.

Long-term extension

The long-term extension enrolled 1803 subjects, mainly from REPRISE (506 from the tolvaptan group, 570 from placebo) and TEMPO 4:4 (718 tolvaptan subjects); 7 subjects entered directly from TEMPO 3:4 (4 tolvaptan and 3 placebo) and 2 from the phase 2 NOCTURNE trial (NCT01451827;
both tolvaptan). A total of 1800 subjects received ≥1 tolvaptan dose in the extension and were included in the safety analysis.\(^4\)

Enrollment criteria for the extension included an eGFR ≥20 mL/min/1.73 m\(^2\) within 3 months of the baseline visit. Subjects with a lower eGFR could be enrolled with medical monitor and sponsor approval and increased frequency of monitoring. Subjects enrolling from REPRISE were initiated on tolvaptan at a split dose of 45/15 mg, with upward titration every 3 to 4 days to 60/30 mg or 90/30 mg per day according to tolerability. TEMPO 4:4 subjects retained the last dose level from TEMPO 4:4 and started at the same dose in the extension.

Cumulative tolvaptan exposure prior to the extension was ≤5 years for TEMPO 4:4 subjects and ~1 year for REPRISE tolvaptan subjects. The trial was planned to continue until the last subject enrolled from REPRISE completed 18 months of tolvaptan treatment in the extension. Monitoring (i.e., liver chemistry) was completed monthly in subjects with <18 months of cumulative tolvaptan exposure, then every 3 months thereafter. All subjects rolling over from REPRISE, however, were monitored monthly in the long-term extension, irrespective of previous treatment assignment, as the blind from REPRISE was still in effect. Once REPRISE was unblinded, subjects who had been randomized to tolvaptan and fulfilled the 18-month cumulative exposure threshold could switch to testing every 3 months. Hepatic safety data from the long-term extension up to February 23, 2019, are included in this analysis.
Table S1. Clinical trial enrollment of subjects prior to entry into TEMPO 4:4 and the long-term extension

<table>
<thead>
<tr>
<th>Study</th>
<th>N (%): TEMPO 4:4</th>
<th>Long-term Extension</th>
<th>N (%): TEMPO 4:4</th>
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<tr>
<td></td>
<td>Tolvaptan</td>
<td>Placebo</td>
<td>Total</td>
</tr>
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<td>TEMPO 2:4a</td>
<td>30 (4.1)</td>
<td>0</td>
<td>30 (2.8)</td>
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<tr>
<td>TEMPO 3:4</td>
<td>557 (75.5)</td>
<td>314 (91.0)</td>
<td>871 (80.4)</td>
</tr>
<tr>
<td>NOCTURNEb</td>
<td>98 (13.3)</td>
<td>31 (9.0)</td>
<td>129 (11.9)</td>
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<tr>
<td>156-06-260c</td>
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<td>10 (0.9)</td>
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<td>22 (3.0)</td>
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<td>NCT01210560e</td>
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</tr>
<tr>
<td>REPRISE</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

aA phase 2, open-label, 3-year trial; bA phase 2, randomized, double-blind, placebo-controlled, 8-week trial; cA short-term, open-label trial; dA phase 2, open-label, 3-week trial; eA phase 2, randomized, double-blind, placebo-controlled, 3-week trial.
References


