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Enclosure:

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TH-PO422

Liver Safety of Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Interim Data from an EU Post-authorization Safety Study (EUPASS)

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BACKGROUND AND OBJECTIVE

- During clinical development of tolvaptan for the treatment of autosomal dominant polycystic kidney disease (ADPKD) in adults with evidence of rapidly progressing disease, a liver safety signal was identified[1]
- To mitigate the risk of liver injury, the European Union (EU) tolvaptan label requires once-monthly liver enzyme monitoring for the first 18 months of treatment and every 3 months thereafter[2]
- Clinical trials and post-marketing surveillance data support once-monthly monitoring for detection and appropriate management of liver enzyme elevations to prevent severe injury[1,3]

To further characterize the liver safety profile of tolvaptan in the post-marketing setting, we performed an interim analysis of the post-authorization safety study (PASS) required as a condition of tolvaptan regulatory approval

METHODS

Design

- A prospective, observational study of patients receiving tolvaptan therapy for ADPKD in the real-world clinical context
- Certified prescribers who complete the required tolvaptan educational training are invited to participate and enroll their patients

Patient Eligibility

- Prescribed tolvaptan for ADPKD by the appropriately certified prescriber
- Tolvaptan-naïve
- Willing and able to provide informed consent or legal guardian consent, understand study requirements, and comply with study and data collection processes

Analysis Period

- The PASS commenced with enrollment of the first patient in October 2016, and the database lock date for this interim analysis was April 15, 2022

Endpoints

- Primary endpoint: incidence of patients with acceptable transaminase levels at screening who experience transaminase elevations (i.e., alanine aminotransferase [ALT] or aspartate aminotransferase [AST] ≥3 x upper limit of normal [ULN]) or an adverse event consistent with hepatotoxicity
- A secondary endpoint is the incidence of patients who meet Hy's Law laboratory criteria (ALT or AST ≥3 x ULN and total bilirubin >2 × ULN in the absence of elevated alkaline phosphatase)

Assessments

- Study data are obtained through physician records collected as part of routine standard of care
- As per the requirements of the tolvaptan EU Summary of Product Characteristics (SmPC), during the first 18 months of tolvaptan therapy, monthly liver function testing is performed. After 18 months of treatment, testing should continue at 3-month intervals
- Patients who develop elevated liver enzyme levels after initiating tolvaptan are to be monitored and managed as outlined in the SmPC, based on the criteria specified there for increased frequency of testing, treatment interruption, and possible permanent discontinuation
- Adverse events that may indicate liver injury were recorded, such as fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, icterus, dark urine, or jaundice

RESULTS

Study Population

- As of data cutoff date (April 15, 2022), 2185 patients were screened for study eligibility, and 2118 enrolled (**Table 1**)
- Of the 2118 enrolled, 2074 (97.9%) participants took at least 1 dose of tolvaptan and were included in the safety analysis population
- The overall mean (standard deviation [SD]) age of participants was 43.0 years (10.5) with 72.9% aged <50 years and 27.1% aged ≥50 years (**Table 1**)
- Nearly equal numbers of male and female participants were enrolled
- Most participants were white (92.1%)
- Baseline chronic kidney disease (CKD) stages in the safety analysis population were predominantly G2 (27.2%), G3a (22.6%), and G3b (23.8%), with smaller percentages in G1 (14.8%), G4 (6.1%), and G5 (3 participants; 0.1%). Tolvaptan is indicated for patients in stages G1-G4 at initiation of treatment

Table 1. Participant Baseline Characteristics

Variable	All Participants (N=2118)	Variable	All Participants (N=2118)
Sex, n (%)		Weight in kg	
Female	1028 (48.5)	Mean (SD)	82.1 (18.1)
Male	1081 (51.0)	Range	34, 175
Sex missing	9 (0.4)	Total kidney volume in ml	
Age in years		Mean (SD)	1933 (1152)
Mean (SD)	43.0 (10.5)	Median	1645
Range	18, 97	Range	13, 8030
Age group in years, n (%)		CKD stage	2074[a]
<50	1543 (72.9)	G1	307 (14.8)
≥50	573 (27.1)	G2	565 (27.2)
Age missing	2 (0.1)	G3a	468 (22.6)
White race, n (%)	1951 (92.1%)	G3b	493 (23.8)
Height in cm		G4	127 (6.1)
Mean (SD)	174.2 (10.3)	G5	3 (0.1)
Range	115, 208	CKD stage missing	111 (5.4)

[a]CKD stage information is for participants who took at least 1 dose of tolvaptan (safety population; n=2074).
CKD, chronic kidney disease; SD, standard deviation.

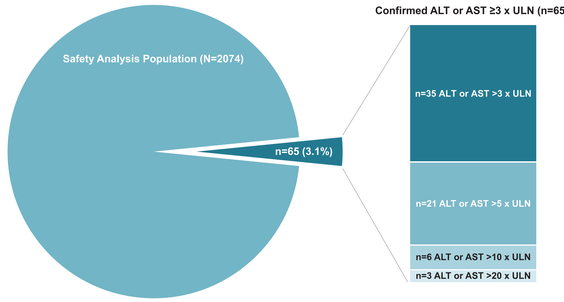
Tolvaptan Exposure

- The overall mean (SD) duration of tolvaptan exposure in the PASS was 631.3 (519.2) days (approximately 21 months), with a range of 1 to 1997 days and a median of 527.5 days
- Most participants (1922/2074, 92.7%) initiated therapy at a starting dose of 60 mg (daily split dose of 45 mg + 15 mg) in accordance with the SmPC

Incidence of Liver Injury

- A total of 223/2074 (10.8%) patients in the safety population experienced ALT or AST ≥3 x ULN or an adverse event consistent with hepatotoxicity
- The group of 223 included 75 (3.6%) with ALT or AST ≥3 x ULN and 200 (9.6%) who had an adverse event consistent with hepatotoxicity (some participants had both)
- Data review of the 75 participants with ALT or AST ≥3 x ULN indicated that further confirmation from the investigational sites was needed for 10 participants. The remaining 65 participants had confirmed ALT or AST ≥3 x ULN (**Figure 1**)

Figure 1. Participants With Confirmed ALT or AST ≥3 x ULN

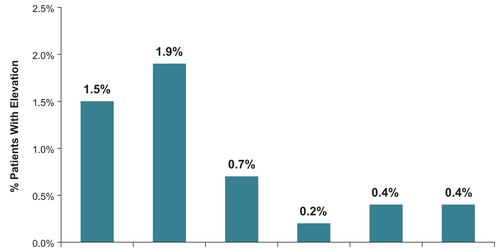


ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal.

Assessment of Liver-Related Adverse Events

- Of the 65 participants with confirmed ALT or AST ≥3 x ULN, 15 experienced only the elevation, and 50 experienced accompanying liver-related adverse events
- Counting by event instead of participant, there were a total of 84 events of confirmed ALT or AST ≥3 x ULN, including 69 events with accompanying liver-related adverse events and 15 with only the transaminase elevation ≥3 x ULN
  - By investigator assessment, most of the 69 liver-related adverse events were mild (41/69; 59.4%), 18 (26.1%) were of moderate severity, and 10 (14.5%) were severe
  - Of the 69 events, investigators considered 63 to be related and 6 unrelated to tolvaptan
- **Figure 2** shows the incidence of elevated ALT or AST by duration of exposure

Figure 2. Incidence of ALT or AST ≥3 x ULN in the Safety Population (n=2074) by Duration of Tolvaptan Exposure



	<6M	6 to <12M	12 to <18M	18 to <24M	24 to <36M	≥36M
Number of patients with elevation	32	28	8	2	3	2
Number of evaluable patients[a]	2074	1474	1218	1003	846	479

[a]The number of patients who were treated with tolvaptan during the time period; the denominator for calculating incidence.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; M, months.

Clinical Management and Outcomes in Participants with Confirmed ALT or AST ≥3 x ULN

- The action taken with tolvaptan in response to the 84 liver-related adverse events and/or ALT or AST elevations ≥3 x ULN in 65 patients included tolvaptan interruption (39 events), tolvaptan withdrawal (20 events), and dose reduction (5 events)
  - Tolvaptan dose was unchanged in 17 events, uptitrated in 1 event, and the action taken was not reported for 2 events
- As recommended per labeling, tolvaptan was interrupted or withdrawn in 59 (90.8%) of 65 patients with confirmed ALT or AST ≥3 x ULN
- At the time of reporting, 66 of the 84 events had resolved, 7 were resolving, 6 events were not resolved, and the outcome of 5 events was not reported
- Tolvaptan was re-initiated in 27 participants who had interrupted treatment, of whom 20 continued the re-initiated tolvaptan for longer than 6 months

Assessment of Severe Liver Injury

- 49 participants experienced elevations in total bilirubin >2 x ULN. However, none of these total bilirubin elevations were accompanied by ALT or AST levels ≥3 x ULN; therefore, there were no cases meeting Hy's Law laboratory criteria
- One participant underwent liver transplant for polycystic liver disease after 278 days of tolvaptan treatment
  - The liver function test results were within normal range throughout the duration of tolvaptan therapy, which was withdrawn at the time of the transplant
  - The investigator assessed the transplant as unrelated to tolvaptan and due to the patient's underlying condition of polycystic liver disease
- No deaths attributable to liver injury occurred

CONCLUSIONS

- In this post-marketing pharmacovigilance study (EUPASS), the proportion of participants with ALT or AST ≥3 x ULN (3.6%) was comparable to the reported frequency of liver enzyme elevations in 2 pivotal clinical trials of tolvaptan (i.e., 4.4-5.6% with ALT >3 x ULN)[1]
  - No cases meeting Hy's Law laboratory criteria and no deaths attributable to liver injury had occurred in EUPASS at time of data cutoff
  - Taken together, these post-marketing data support the effectiveness of per-label once-montly testing for the first 18 months of tolvaptan treatment and every 3 months thereafter to promptly detect liver enzyme elevations and take appropriate action to prevent severe injury
- Results from this study are consistent with earlier findings that the risk for liver function abnormality is highest in the first 18 months of treatment
  - Only approximately half of the EUPASS participants had follow-up beyond 18 months, which must be considered a limitation to this conclusion
- Data collection and verification are ongoing, with the possibility that data on the outcomes of liver injury cases will be revised when the study is final

REFERENCES

1. Alpers DH et al. *Am J Kidney Dis*. 2023;81(3):281-293.e1.
2. Jinarc [Summary of Product Characteristics]. Otsuka Pharmaceutical Netherlands B.V. https://www.ema.europa.eu/en/medicines/human/EPAR/jinarc. Accessed September 1, 2022.
3. Estilo A et al. *Clin Kidney J*. 2022;15;1553–1561.

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