Preliminary Results From a European Post-authorisation Study to Assess the Safety of Paxlovid Among Patients With Moderate or Severe Hepatic or Renal Impairment

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BACKGROUND

- Paxlovid is an oral antiviral licensed in January 2022 in Europe to treat COVID-19 in patients who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19.[1] Here, we describe results of an interim analysis from a post-authorisation safety study (PASS) to assess the safety of Paxlovid in populations with hepatic or renal impairment not studied in clinical trials.
- This PASS (EU PAS number: EUPAS50123) is a commitment to the European Medicines Agency (EMA).

OBJECTIVE

- The objective of this PASS is to assess the safety of Paxlovid in persons with moderate or severe hepatic or renal impairment and the adverse events resulting from medication overexposure potentially related to hepatic or renal impairment.

METHODS

Data Sources

Table 1. Data Sources and Study Period Used in the Interim Analysis

Data source	Data available for the study period	Start and end dates of study period
Clinical Practice Research Datalink (CPRD) Aurum, UK	Individual-level general practitioner data (hospital data not available for the study period)	1 January 2022 through 31 January 2024
Information System for Research in Primary Care (SIDIAP), Spain	Individual-level general practitioner and hospital data	28 January 2022 through 31 December 2023
French Administrative Healthcare Database (SNDS),[a] France	Aggregated Open Medic outpatient community pharmacy data from publicly available information	28 January 2022 through 31 December 2023

SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, Catalonia, Spain; SNDS = Système National des Données de Santé; UK = United Kingdom.

[a] Aggregated publicly available data were obtained because individual-level data extraction approval was not available at the time of analysis.

Study Population and Follow-Up

- Patients with moderate or severe hepatic impairment and moderate or severe renal impairment were identified through diagnosis codes recorded ever before or at the date of first exposure ever, that is, at time zero (in SIDIAP and in CPRD) and through laboratory values recorded within 18 months before or at time zero (only available in CPRD). Information on renal and hepatic impairment was not available in SNDS.
- Eligibility criteria are presented as part of the cohort attrition in **Figure 1.**
- Follow-up started the date of first exposure ever (time zero) and ended at the earliest of 30 days after time zero, end of study period (**Table 1**), occurrence of outcome(s) (**Table 2**), disenrollment, or death.

Exposure

- **Study medication:** Paxlovid
- **Active comparators** are medications indicated for the treatment of COVID-19, as available: molnupiravir, remdesivir, tixagevimab/cilgavimab, anakinra, regdanvimab, tocilizumab, casirivimab/imdevimab, and sotrovimab. No active comparators were available for this interim analysis in SIDIAP.

Outcomes

Table 2. Primary Outcomes

Type of outcome	Outcomes
Prespecified[a]	• Hepatic transaminase elevations, clinical hepatitis, or jaundice • Severe nausea, vomiting, diarrhoea, or abdominal pain • Dysgeusia • Headache • Hypertension • Anaphylactic reactions
Data-driven	• Diagnoses and symptom codes recorded within 30 days after exposure to Paxlovid

[a] Ascertained based on diagnoses and medications. Patients with a history of the specific outcome of interest during the 30 days (365 days for headache and hypertension) before time zero were excluded from each outcome-specific analysis.

Common Data Model

- The ConcePTION common data model[2] and common descriptive analytics were used to generate the counts in SIDIAP and CPRD.

Analysis

This interim analysis aimed to describe:

- Aggregated counts of eligible Paxlovid-exposed patients, patients exposed to comparator medications as available in each data source, and aggregated outcome counts from SIDIAP (Spain) and the CPRD (UK).
- Aggregated counts of sold boxes and users, by age group and sex, for Paxlovid and comparator medications that were in use in the general population in SNDS (France). This is because aggregated publicly available data from Open Medic were used for SNDS from which renal and hepatic impairment could not be identified.

According to small cell count restriction rules in CPRD, counts between 1 and 4 (both ends included) have been masked as 1≤n≤4, and any other descriptive data that could allow back-calculation to a small count have been suppressed or masked as not reportable.

RESULTS

Patient Counts

- In **SNDS**, 206,069 patients in the general population in years 2022 and 2023 had ≥ 1 dispensing for Paxlovid (≈ 70% aged ≥ 60 years, > 55% female); fewer patients used anakinra (5895; ≈ 40% aged ≥ 60 years, ≈ 50% female) or tocilizumab (22,306; ≈ 60% aged ≥ 60 years, ≈ 70% female). Each year, patients were dispensed, on average, approximately 1 box of Paxlovid and 7 and 20 boxes for tocilizumab and anakinra, respectively (**Table 3**).
- **Figure 1** presents cohort attrition in **SIDIAP** and **CPRD**:
  - The most common reason for exclusion in SIDIAP and CPRD was not fulfilling the criteria for inclusion in the hepatic or renal impairment populations.
  - In **CPRD**, the active comparator that most frequently fulfilled the eligibility criteria was molnupiravir, followed by sotrovimab.
- In CPRD, remdesivir and tocilizumab were the active comparators for which the criterion of "having a COVID-19 diagnosis within 7 days before the first prescription" was infrequently fulfilled (i.e., 29.7% and 2.1% of patients, respectively).

Table 3. Number of Patients With at Least 1 Dispensing for Paxlovid or Active Comparator Medications and Number of Dispensed Boxes (SNDS, 2022-2023)

	2022			2023		
Medication	**Patients**	**Boxes**	**Boxes per patient[a]**	**Patients**	**Boxes**	**Boxes per patient[a]**
Paxlovid	**83,102**	**85,164**	**1.0**	**122,967**	**126,596**	**1.0**
Tocilizumab	9961	68,738	6.9	12,345	87,407	7.1
Anakinra	2724	57,013	20.9	3171	61,492	19.4

Note: Data for years 2022 and 2023 are sourced from Open Medic.
[a] Boxes per patient are calculated by dividing the number of dispensed boxes by the number of patients. A higher number of boxes dispensed per patient suggests that the medication is used for a chronic indication and not for COVID-19.

Figure 1. Cohort Attrition for the Moderate or Severe Hepatic/Renal Impairment Study Populations in SIDIAP and CPRD Aurum

Paxlovid and active comparators	SIDIAP (Spain) Paxlovid N %	CPRD Aurum (UK) Paxlovid N %	Molnupiravir N %	Anakinra N %	Remdesivir N %	Sotrovimab N %	Tocilizumab N %
Source populations							
Paxlovid or active comparator prescribed/dispensed during the study period	3535	626	433	77	122	200	844
First prescription/dispensing of Paxlovid or active comparator with prior COVID-19 diagnosis[a]	3535 100%	605 96.6%	411 94.9%	72 93.5%	111 91.0%	195 97.5%	808 95.7%
Eligibility criteria (at time zero[b])							
COVID-19 documented within 7 days before and including time zero	3181 90.0%	439 72.6%	296 72.0%	0 0%	33 29.7%	147 75.4%	17 2.1%
No prescription/dispensing of Paxlovid or any active comparator[c] within 90 days before and including time zero	3535 100%	594 98.2%	400 97.3%	70 97.2%	109 98.2%	193 99.0%	805 99.6%
At least 12 months of data before and including time zero	3495 98.9%	574 94.9%	390 94.9%	61 84.7%	101 91.0%	184 94.4%	729 90.2%
No missing age or sex data before and including time zero	3535 100%	605 100%	411 100%	72 100%	111 100%	195 100%	808 100%
At least 1 day of follow-up including time zero	3535 100%	605 100%	411 100%	72 100%	111 100%	195 100%	808 100%
Moderate or severe **hepatic** impairment before and up to COVID-19 diagnosis and time zero[d]	39 1.1%	1≤n≤4 NR	1≤n≤4 NR	1≤n≤4 NR	1≤n≤4 NR	7 3.6%	5 0.6%
Moderate or severe **renal** impairment before and up to COVID-19 diagnosis and time zero[d]	592 16.7%	56 9.3%	79 19.2%	1≤n≤4 NR	24 21.6%	54 27.7%	82 10.1%
Met all eligibility criteria for the hepatic impairment population[e]	35 1.0%	0	1≤n≤4 NR	0	0	7 3.6%	0
Met all eligibility criteria for the renal impairment population[e]	560 15.8%	37 5.9%	49 11.3%	0	5 4.1%	32 16.0%	1≤n≤4 NR

NR = not reportable.

Note: Presented are medications for which records were present in the data source for the study population. In Spain, molnupiravir was not dispensed, and in SIDIAP, no active comparators were available for this analysis.

[a] Counts of the number of patients who had a first prescription/dispensing of Paxlovid or an active comparator with a prior COVID-19 diagnosis. The denominator is the total in the first row.

[b] The different eligibility criteria were applied independently and are not mutually exclusive. The denominator is the total in the second row.

[c] Active comparators: 1≤n≤4 users of casirivimab/imdevimab were identified in CPRD.

[d] Counts of patients with moderate or severe hepatic impairment occurring before and up to the dates of a documented COVID-19 diagnosis and first exposure to Paxlovid.

[e] The denominator is the total in the first row.

Outcome Counts

- In **SIDIAP**, of the 35 Paxlovid users with hepatic impairment, 1 (2.9%) had hepatic transaminase elevations postexposure. Similarly, of the 560 users with renal impairment, 4 (0.7%) had headaches and 23 (7.6%) had hypertension postexposure.
- In **SIDIAP**, of the 23 patients with hypertension diagnoses after Paxlovid exposure and no hypertension diagnosis in the 365 days before time zero, 18 (78%) had a diagnosis of hypertension before Paxlovid exposure (i.e., from 366 days before time zero to ever before), and all had records for dispensings of antihypertensive medications in the 365 days before Paxlovid exposure. This suggests that all patients had prior hypertension and that hypertension was not due to Paxlovid exposure.
- In **CPRD**, no Paxlovid users had hepatic impairment. Of the 37 Paxlovid users with renal impairment, 1≤n≤4 had severe abdominal pain and 1≤n≤4 had a headache after exposure.
- In both **SIDIAP** and **CPRD**, data-driven outcomes were mostly related to COVID-19, such as respiratory infections and symptoms.

CONCLUSIONS

- The small number of Paxlovid-exposed patients with moderate or severe hepatic or renal impairment was expected given the short study period and the low prevalence of Paxlovid use in these populations, which aligns with recommendations from the EU and UK summaries of product characteristics (SmPCs). The number of eligible patients receiving Paxlovid in SNDS will be assessed in future analysis.
- Overall, the observed number of outcomes was low, and the high frequency of hypertension in SIDIAP in patients with renal impairment was likely driven by the inclusion of prevalent hypertension events.

DISCLOSURES

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