Clinical Study Protocol

EU PAS Number: EUPAS1000000006

Title: Retrospective chart review of safety outcomes associated with use of maribavir in patients with post-transplant refractory cytomegalovirus (CMV) infection and comorbid end-stage renal disease (ESRD) or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis

Study Number: TAK-620-4007

Document Version and Date: Version 1.0, 02 June 2023

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

NONINTERVENTIONAL SAFETY STUDY PROTOCOL

Study title: Retrospective chart review of safety outcomes associated with use of maribavir in patients with post-transplant refractory cytomegalovirus (CMV) infection and comorbid end-stage renal disease (ESRD) or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis

Study number: TAK-620-4007

Version number: V 1.0, 02 June 2023

Ethics statement: This study will be conducted in compliance with the protocol, the Declaration of Helsinki, International Society for Pharmacoepidemiology Guidelines for Good Epidemiology Practices, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Guidelines for Methodological Standards in Pharmacoepidemiology, Good Pharmacovigilance Practices, and all applicable regulatory requirements.

Signature page

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Study number: TAK-620-4007

Version number: V 1.0, 31 May 2023

Marketing Authorization Holder: Takeda Pharmaceuticals International AG Ireland Branch

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Signature	DocuSigned by: [redacted]	**Date (DD-MMM-YYYY)**	05-Jun-2023 | 20:48:21 CEST

Investigator:

By signing below, the investigator acknowledges that he/she has read and understands this protocol, understands and abides by the requirements for maintenance of source documentation, and provides assurance that this study will be conducted according to all requirements as defined in this protocol, Clinical Trial Agreement, good pharmacovigilance practices, and all applicable regulatory requirements. If applicable, he/she will comply with the requirements for obtaining informed consent from all study patients prior to initiating any protocol-specific procedures and for obtaining written initial and ongoing ethics committee(s) protocol review and approval.

Role		**Printed Name**	
Signature		**Date (DD-MMM-YYYY)**	

STUDY INFORMATION

Title	Retrospective chart review of safety outcomes associated with use of maribavir in patients with post-transplant refractory cytomegalovirus (CMV) infection and comorbid end-stage renal disease (ESRD) or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis
Protocol number	TAK-620-4007
Protocol version identifier	V 1.0
Date of last version of protocol	31 May 2023
EU PAS register number	Study will be registered in EU Post Authorization Study (PAS) Register following Pharmacovigilance Risk Assessment Committee (PRAC) approval of final protocol and before study initiation.
Active substance	Maribavir (Anatomical Therapeutic Chemical (ATC) code: J05AX10)
Medicinal product	LIVTENCITY™
Product reference	European Union (EU) marketing authorization number: EMEA/H/C/005787
Procedure number	EU/1/22/1672/001-003
Joint PASS	No
Research question and objectives	**Research question:** • What is the safety profile of maribavir for treating post-transplant cytomegalovirus (CMV) infection in patients with end-stage renal disease (ESRD) or severe chronic renal disease requiring peritoneal dialysis or hemodialysis? **Primary objective:** • To characterize the safety of maribavir as prescribed in routine clinical practice in terms of occurrence of adverse events (AE) in patients with post-transplant refractory CMV infection and comorbid ESRD or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis. **Secondary objective:** To assess the occurrence of AEs of special interest (AESI): • Immunosuppressant drug concentration level increased • Tissue-invasive CMV disease

	• Relapse or progression of the underlying disease for which the transplant was performed • Taste disturbance (dysgeusia) • Nausea • Vomiting • Diarrhea • Invasive fungal or bacterial infections • Graft-versus-host-disease (GVHD)
Countries of study	The study will include approximately nine countries in Europe. The list of countries is not final, but the following countries will be considered for inclusion: • Austria • Belgium • Denmark • Estonia • France • Germany • Italy • Spain • United Kingdom
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LIST OF ABBREVIATIONS

Abbreviations	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
CI	confidence interval
CMV	cytomegalovirus
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
EC	ethics committee
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESRD	end-stage renal disease
EU	European Union
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
GVHD	graft-versus-host-disease
HSCT	hematopoietic stem cell transplantation
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PASS	post-authorization safety study
PT	preferred term
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
SOT	solid organ transplant

RESPONSIBLE PARTIES

Principal Investigator	N/A
Co-investigator Other responsible parties	N/A

The final list of investigators will be provided in the final study report and can be supplied as an appendix to this protocol.

1. ABSTRACT

Title

Retrospective chart review of safety outcomes associated with use of maribavir in patients with post-transplant refractory cytomegalovirus (CMV) infection and comorbid end-stage renal disease (ESRD) or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis.

Rationale and Background

CMV infection is a common post-transplantation complication in patients treated with immunosuppressive drugs following hematopoietic stem cell transplantation (HSCT) or solid organ transplant (SOT) (Hiskey et al. 2022; Ramanan and Razonable 2013). Although conventional systemic anti-CMV agents are generally effective, their use is limited by their respective toxicities, including bone marrow suppression and renal impairment, which are of particular concern in transplant patients (Boeckh et al. 2003; Ljungman et al. 2001; Reusser et al. 2002; Salzberger et al. 1997).

Maribavir can be used to treat refractory/resistant CMV infection. Phase 2 and 3 studies have been conducted in HSCT and SOT patients that demonstrated the safety of maribavir in the treatment of post-transplant CMV disease (Avery et al. 2022; Papanicolaou et al. 2019). On 09 Nov 2022, LIVTENCITY (maribavir) was granted marketing authorization valid throughout Europe for the treatment of CMV infection and/or disease that is refractory (with or without resistance) to one or more prior therapies in adults who have undergone HSCT or SOT (ema.europa.eu/en/medicines/human/EPAR/livtencity, Livtencity, Accessed 22 March 2023).

There is no available safety information with the use of maribavir in subjects with post-transplant refractory CMV infection and comorbid ESRD or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis, as the Phase 3 clinical studies SHP620-302 and SHP620-303 (Avery et al. 2022) excluded subjects with estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m2 according to the Modification of Diet in Renal Disease (MDRD) formula for adults (Levey et al. 2006) or the Schwartz formula for subjects <18 years of age (Schwartz et al. 1976). However, patients with ESRD and patients with severe chronic renal disease requiring peritoneal dialysis or hemodialysis have an impaired immune response, which puts them at a higher risk of a CMV infection. CMV disease is associated with graft vs. host disease (GVHD) and graft rejection following HSCT or SOT (Cantoni et al. 2010; Razonable 2010).

Use of maribavir in patients with ESRD including peritoneal dialysis or hemodialysis is considered as missing information in the European Union (EU) Risk Management Plan (RMP) (Takeda 2022, EU Risk Management Plan (RMP) for Livtencity (Maribavir) V0.7). To gain knowledge on the safety outcomes of this missing information, a retrospective chart review is proposed as an additional pharmacovigilance activity (EU RMP category 3).

This observational study is designed to assess the safety of maribavir for the treatment of refractory CMV infections in HSCT and SOT recipients among patients with ESRD, including patients with severe chronic renal disease requiring peritoneal dialysis or hemodialysis, in

real-life conditions in the post-commercialization phase, as reported by the treating physicians. This study will also evaluate the occurrence of adverse events of special interest (AESIs), which have been recorded in the SHP620-303 trial protocol (Avery et al. 2022).

Research Question and Objectives

Research question:

- What is the safety profile of maribavir for treating post-transplant CMV infection in patients with ESRD or severe chronic renal disease requiring peritoneal dialysis or hemodialysis?

Primary objective:

- To characterize the safety of maribavir as prescribed in routine clinical practice in terms of occurrence of adverse events (AEs) in patients with post-transplant refractory CMV infection and comorbid ESRD or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis.

Secondary objective:

To assess the occurrence of AESIs:

- Immunosuppressant drug concentration level increased
- Tissue-invasive CMV disease
- Relapse or progression of the underlying disease for which the transplant was performed
- Taste disturbance (dysgeusia)
- Nausea
- Vomiting
- Diarrhea
- Invasive fungal or bacterial infections
- GVHD

Study Design

This is an observational, multicountry, retrospective, post-authorization safety study (PASS) based on the review of secondary data collected from medical records of transplant recipients treated with maribavir who are refractory to prior anti-CMV treatment and have comorbid ESRD or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis. This study does not interfere with standard medical care and will not impact the treatment of the study participants.

The current study involves a review of routine clinical information available in the medical charts of eligible patients. Physicians will be asked to include all eligible patients until the study meets the expected sample size. Chart reviews will be performed regardless of the patients' survival status at the time of data abstraction.

The study design will include a follow-up period covering the full duration of the treatment course with maribavir from the index date (Day 0: the day of initiation of the first maribavir treatment course during the eligibility period) until the earliest of death, end of data availability, treatment discontinuation, or end of treatment+7 days post-treatment. An additional 7-day grace period following treatment discontinuation or the end of treatment is allowed to capture potentially relevant events that may occur in the immediate period after the censoring event.

The eligibility period is defined as the period of time within which the index date must fall for the patient to be included in the study. The index date should have occurred between the commercial launch date of maribavir and at least 3 months before the first data abstraction. These dates will be different for each country. Data collection will span 2 main periods of time anchored to the date of the index event:

- Pre-index event period: begins on the date of diagnosis of kidney disease or underlying health issue that leads to the transplant and ends 1 day before the index date during the eligibility period
- Post index event period: begins 1 day after the index date during the eligibility period and ends at the earliest of death, completion of maribavir treatment+7 days post-treatment completion, maribavir discontinuation for any reason+7 days post-treatment discontinuation, or the end of data availability

The primary endpoint is the incidence of any AE. The secondary endpoint is the incidence of an AESI.

Population

The study cohort will comprise European patients aged ≥18 years who have undergone SOT or HSCT, who have been diagnosed with refractory CMV during the post-transplant period, and who have comorbid ESRD or with severe chronic renal disease requiring peritoneal dialysis or hemodialysis.

Sites will be selected from countries in Europe including Austria, Belgium, Denmark, Estonia, France, Germany, Italy, Spain, and the United Kingdom.

Variables

Patient demographics

- Year of birth
- Sex
- Ethnicity/race
- Age at maribavir treatment initiation

Medical history and disease characteristics

- Date of chronic kidney disease diagnosis
- ESRD characteristics
    - Date of ESRD diagnosis

  - Etiology of ESRD
  - eGFR at ESRD diagnosis

- Dialysis history
  - Type of dialysis
  - Start/end dates of dialysis

- CMV infection
  - Previous CMV infection(s)
    - Date of onset of infection/diagnosis
    - Refractory characteristics
      - Antiviral agent to which CMV infection is refractory
      - Type of drug-resistant mutations (if applicable)
    - Classification of CMV infection
    - Previous anti-CMV prophylaxis and treatment
    - AEs including renal toxicity from previous anti-CMV treatment
  - Current CMV infection*
    - Date of onset of infection/diagnosis
    - Refractory characteristics
      - Antiviral agent to which CMV infection is refractory
      - Type of drug-resistant mutations (if applicable)
    - Classification of CMV infection
    - Treatment and prophylaxis for CMV infection
    - CMV status (resolved, unresolved)

*Current CMV infection and current transplant refer to the latest CMV infection and transplant for which the maribavir treatment was initiated.

- Transplants
  - Previous transplant(s)
    - Type of transplant(s)
    - Date of transplant(s)
    - Number of transplant(s)
    - Reason for transplant(s)
    - Stem cell source (for HSCT)
    - CMV serostatus
  - Current transplant*
    - Type of transplant
    - Date of transplant
    - Reason for transplant
    - Stem cell source (for HSCT)
    - CMV serostatus

- GVHD status at index (for HSCT patients only)
  - Acute GVHD status at index date
  - Chronic GVHD status at index date

- Relevant comorbidities present at index

Maribavir treatment initiation at index

- Start date of maribavir treatment
- Daily dose at initiation

Maribavir treatment regimen post index

- Changes in treatment regimen
  - Date of change
  - New daily dose
  - Reason for change
- Treatment completion or discontinuation
  - Date of treatment completion
  - Date of discontinuation
  - Reason of discontinuation

Concomitant medications during maribavir treatment

- Drug name
- Start/end dates

Dialysis treatment during maribavir treatment

- Type and frequency
- Changes in dialysis treatment
  - Reason for change

AEs (including a 7-day safety follow-up after the end of maribavir treatment) or treatment discontinuation

- AE/AESI description
- Start/end dates
- Serious/nonserious AE
- AE severity
- Outcome of AE
- Relatedness to maribavir

Patient status

- Death
  - Date of death
  - Primary cause of death/Relatedness
- Lost to follow-up
  - Date of loss to follow-up

Data sources

Individual patient-level data will be abstracted from patient medical records and entered into an electronic data capture (EDC) system by trained local site staff.

Study size

Approximately 10 patients will be included. The sample size is based on practical considerations and depends significantly on the market utilization of maribavir in the target countries. It is also supported by a precision-based approach for different AE rates (see Section 6.5).

Data analyses

The analyses will be descriptive. Continuous variables will be described by the number of eligible participants and missing data, mean, standard deviation, median, first quartile, third quartile, and minimum and maximum values. Categorical variables will be described as the total number of participants and relative percentage per category. Two-sided 95% confidence intervals (CIs) will be reported as appropriate. There will be no imputation of missing data.

The incidence of all AEs and AESIs that have occurred from the index date (start of maribavir) until 7 days following maribavir discontinuation or treatment completion will be presented. An overall summary will be presented consisting of the number and percentage of patients experiencing at least 1 AE or AESI. All safety events will also be summarized by system organ class (SOC) and Preferred Term (PT).

The incidence rates (number of first events per person-year at risk) of AEs and AESIs (overall and by SOC and PT) will be computed along with 95% CIs. The number and percentage of patients with AEs, total number of AEs, and AE rate (total number of each event per person-year) will also be summarized.

Milestones

- Registration in the EU electronic Register of Post Authorization Studies: January 2024
- Start of data collection: June 2025*
- Progress report: September 2025
- End of data collection: January 2027
- Final report of study results: January 2028

*Timelines are conditional on the actual date of market entry in each country. This is a retrospective study, and patient data accrual will be occurring from the first maribavir launch up to the start of data collection.

2. AMENDMENTS AND UPDATES

Number	Date	Section of Study Protocol	Amendment or Update	Reason
Not applicable				

3. MILESTONES

Sites are expected to perform a first retrospective data collection from medical charts approximately in June 2025 (start of data collection) and a second one approximately in November 2026. Data extraction and quality control review is expected to take sites approximately 2 months to complete. Preparation of a progress report is expected to take another 1-2 months, resulting in progress report submission in September 2025. All study data will be available for analyses in January 2027 after data lock point and data cleaning completion (end of data collection). The final study report is expected to be ready for submission in January 2028. Based on the above, the milestones are summarized in Table 1.

Table 1 Study Milestones

Milestone	Planned Date
Registration in the European Union Post Authorization Study Register	January 2024
Start of data collection*	June 2025
Progress report	September 2025
End of data collection	January 2027
Final report of study results	January 2028

[redacted] The data extracted in June 2025 in which the progress report will be based, will be dependent on country-specific launch/ reimbursement date, which means that for some countries the presented data might be less than for other countries. This is a retrospective study, and patient data accrual will be occurring from the first maribavir launch up to the start of data collection. All milestone dates are estimates and are subject to change pending the timing of study start-up and the duration of study activities.

[redacted]

4. RATIONALE AND BACKGROUND

Cytomegalovirus (CMV) is a ubiquitous, beta herpes virus that commonly infects humans. Primary infection with CMV is typically asymptomatic (Razonable and Humar 2013). Serologic evidence of prior infection can be found in 40-100% of adults (de la Hoz et al. 2002). However, serious CMV infection occurs almost exclusively in individuals with compromised immune systems. CMV remains a significant problem for patients undergoing various types of transplants that are associated with the use of potent immunosuppressive chemotherapy, including hematopoietic stem cell transplantation (HSCT) and solid organ transplant (SOT) (de la Hoz et al. 2002; Razonable and Emery 2004).

Recipients who are seropositive at the time of transplant are at greatest risk for symptomatic CMV infection (Cho et al. 2019). Without prophylaxis, approximately 80% of CMV-seropositive patients experience CMV infection after allogeneic HSCT (Ramanan and Razonable 2013).

Although conventional systemic anti-CMV agents (eg, ganciclovir, valganciclovir, intravenous [IV] foscarnet, and IV cidofovir) are generally effective, their use is limited by their respective toxicities, including bone marrow suppression caused by ganciclovir or valganciclovir and renal impairment caused by foscarnet or cidofovir (Boeckh et al. 2003; Ljungman et al. 2001; Reusser et al. 2002; Salzberger et al. 1997). These toxicities are of particular concern in transplant patients in whom the bone marrow has been ablated or significantly suppressed (HSCT patients), who receive ongoing immunosuppressants to prevent organ rejection (SOT patients) or graft vs. host disease (GVHD) (in HSCT patients), or who may require the use of other therapies that are potentially toxic to the kidneys or other organs (SOT and HSCT patients). Development of antiviral resistance is also an ongoing clinical problem in SOT and HSCT that leads to graft loss and even mortality for some transplant patients (Avery 2007; Limaye et al. 2000).

Maribavir is an orally available benzimidazole riboside approved to treat resistant or refractory CMV infections in patients who received a transplant. Maribavir is active against CMV strains that are resistant to conventional antiviral therapies such as ganciclovir, foscarnet, or cidofovir (Chou et al. 2019; Drew et al. 2006). Phase 2 and Phase 3 studies have been conducted to demonstrate the safety, tolerability, and antiviral activity of maribavir for the treatment of resistant or refractory CMV infections in transplant recipients (Avery et al. 2022; Papanicolaou et al. 2019). The Phase 2 trial supported the safety and tolerability of maribavir for a treatment duration of up to 24 weeks (Papanicolaou et al. 2019). The Phase 3 trials administered maribavir for 8 weeks and followed the patients for another 12 weeks after the end of treatment (Avery et al. 2022). The Phase 3 trial concluded that maribavir was superior to the investigator-assigned therapy based on primary endpoint of CMV clearance at Week 8 in transplant recipients with resistant or refractory CMV infection (55.7% vs 23.9% for maribavir and investigator-assigned therapy respectively; adjusted difference [95% confidence interval (CI)]: 32.8% [22.80–42.74]; P <.001). Adverse events (AEs) were most commonly associated with gastrointestinal disorders (eg, diarrhea, dysgeusia, nausea, and vomiting). There were no signals of clinically significant effects of maribavir on vital signs, electrocardiogram parameters, or laboratory findings in the studies conducted for CMV prophylaxis.

On 09 Nov 2022, LIVTENCITY (maribavir) was granted marketing authorization that is valid throughout European Economic Area for the treatment of CMV infection and/or disease that is refractory (with or without resistance) to one or more prior therapies in adults who have undergone HSCT or SOT (ema.europa.eu/en/medicines/human/EPAR/livtencity, Livtencity, Accessed 22 March 2023). On 23 Nov 2021, the US Food and Drug Administration (FDA) approved maribavir for the treatment of refractory (with or without resistance) post-transplant CMV infection/disease in patients aged ≥12 years.

The phase I Study 1263-101 investigated the pharmacokinetics of a single dose of 400 mg maribavir in participants with normal renal function and those with different levels of renal impairment. No statistically significant difference was found between participants with normal renal function (creatinine clearance [CrCl] >80 mL/min) and participants with renal impairment classified according to the Cockcroft-Gault formula (Sampson and Drury 1992) as mild to (50-80 mL/min), moderate (30-49 mL/min), or severe renal impairment (<30 mL/min) (Swan et al. 2007).

Subjects with estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) formula for adults (Levey et al. 2006) or the Schwartz formula for subjects <18 years of age (Schwartz et al. 1976) were excluded from the phase III clinical studies of maribavir for the treatment of post-transplant CMV infection, SHP620-302 and SHP620-303 (Avery et al. 2022). However, patients with end-stage renal disease (ESRD) and patients with severe chronic renal disease requiring peritoneal dialysis or hemodialysis have an impaired immune response, which puts them at a higher risk of a CMV infection. The infection is usually introduced by a blood transfusion or kidney transplant, but may also be a primary infection (Tofiq et al. 2019). This infection is a problem for patients with ESRD, as CMV disease is associated with GVHD and graft rejection following HSCT or SOT (Cantoni et al. 2010; Razonable 2010). Racial disparities have been observed in the risk of developing ESRD. The Black population has a disproportionate risk of developing ESRD compared to the White population, even when adjusting for baseline kidney function and other confounders (Bock et al. 2019).

To date, evidence of maribavir safety is lacking in patients with post-transplant refractory CMV infection and either an eGFR <15 mL/min or an eGFR <30 mL/min receiving peritoneal dialysis or hemodialysis, and this is considered missing information in the European Union (EU) Risk Management Plan (RMP) (Takeda 2022, EU Risk Management Plan (RMP) for Livtencity (Maribavir) V0.7).

This observational (noninterventional) study is designed to assess the safety of maribavir for the treatment of refractory CMV infections in HSCT and SOT recipients among patients with ESRD and patients with severe chronic renal disease requiring peritoneal dialysis or hemodialysis in real-life conditions in the post-commercialization phase, as reported by the treating physicians. This study will also evaluate the occurrence of adverse events of special interest (AESIs), which have been recorded in the SHP620-303 trial protocol (Avery et al. 2022).

5. RESEARCH QUESTION AND OBJECTIVES

Research question:

This study aims to address Takeda's EU RMP commitment to assess the safety of maribavir in patients with ESRD and patients with severe chronic renal disease requiring peritoneal dialysis or hemodialysis. The research question is:

- What is the safety profile of maribavir for treating post-transplant CMV infection in patients with ESRD or severe chronic renal disease requiring peritoneal dialysis or hemodialysis?

Primary objective:

- To characterize the safety of maribavir as prescribed in routine clinical practice in terms of occurrence of AEs in patients with post-transplant refractory CMV infection and comorbid ESRD or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis.

Secondary objective:

To assess the occurrence of AESIs:

- Immunosuppressant drug concentration level increased
- Tissue-invasive CMV disease
- Relapse or progression of the underlying disease for which the transplant was performed
- Taste disturbance (dysgeusia)
- Nausea
- Vomiting
- Diarrhea
- Invasive fungal or bacterial infections
- GVHD

6. RESEARCH METHODS

6.1 Study Design

This is an observational, multicountry, retrospective, post-authorization safety study (PASS) based on the secondary data collected from medical records of transplant recipients treated with maribavir who are refractory to prior anti-CMV treatment and are diagnosed with ESRD or severe chronic renal disease requiring peritoneal dialysis or hemodialysis.

The study does not interfere with standard medical care and will not impact the current treatment of the study participants.

Physicians will be asked to screen existing medical records and consecutively include eligible patients until the study meets the expected sample size. Chart reviews will be performed regardless of the patients' survival status at the time of initiation of data abstraction.

The study design will include a study follow-up period covering the full duration of the treatment course with maribavir from index date (Day 0: the day of initiation of the first maribavir treatment course during the eligibility period) until death, end of data availability, end of treatment or treatment discontinuation +7 days post-treatment, whichever occurs earliest. An additional 7-day grace period following treatment discontinuation or end of treatment is allowed to capture potentially relevant events that may occur in the immediate period after the censoring event.

Eligibility period is defined as the period of time within which the index date must fall for the patient to be included in the study. Index date should have occurred between the commercial launch date of maribavir and 3 months before the first data abstraction. These dates will be different for each country. Data collection will span 2 main periods of time anchored to the date of index event:

- Pre-index event period: begins on the date of diagnosis of kidney disease or underlying health issue that leads to the transplant and ends 1 day before the index date during the eligibility period
- Post index event period: begins on 1 day after the index date during the eligibility period and ends at the earliest of death, completion of maribavir treatment+7 days post-treatment completion, maribavir discontinuation for any reason+7 days post-treatment, or end of data availability

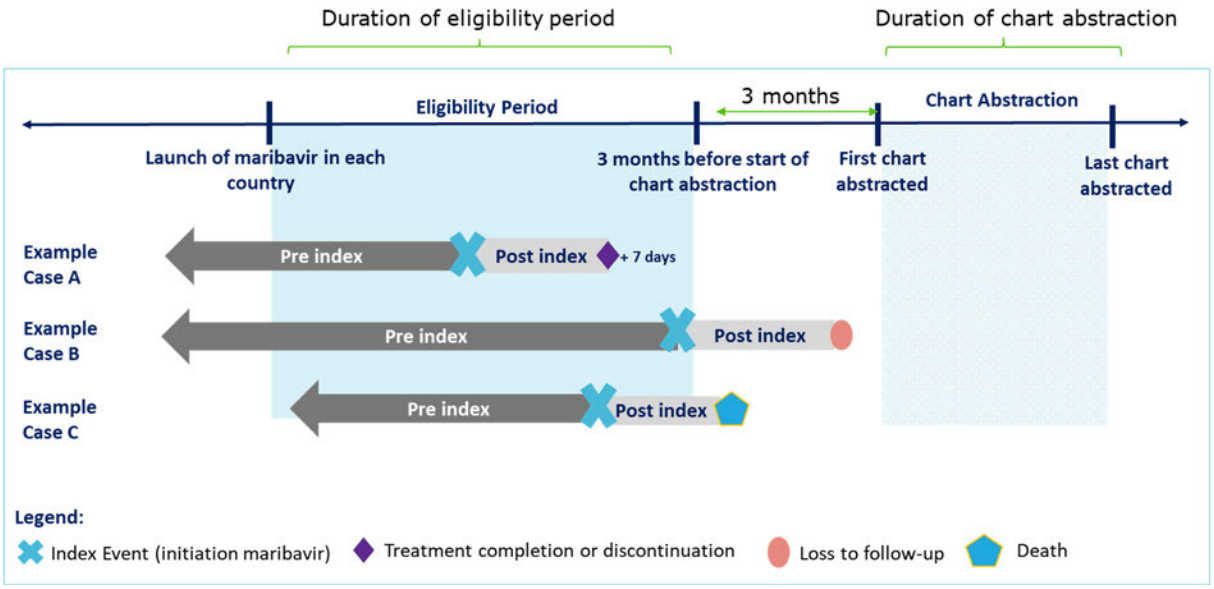
Data from the patient's medical records will be abstracted by study investigators routinely involved in the care and treatment of the target indication (or delegates at the study site). Pseudoanonymous patient-level data will be transcribed, onto electronic case report forms (CRFs) to capture (i) baseline characteristics during the pre-index event period (eg, demographics, comorbidities, disease characteristics, treatment history) and (ii) follow-up data during the post index event period (eg, treatment patterns and safety events).

The primary endpoint is the incidence of any AE. The secondary endpoint is the incidence of the AESIs. The primary and secondary endpoints will be collected as part of the safety events in the post index event period. More details on the study endpoints are provided in Section 6.7.

Before study commencement, the protocol and relevant study documents approval will be obtained from an institutional review board (IRB) or ethics committee (EC). Participants must provide written informed consent before their inclusion in the study, as applicable. IRB/EC approval of a waiver of informed consent will be sought to allow record reviews of deceased patients.

A study design schematic is presented in Figure 1.

Figure 1 Study Design Schematic



6.2 Setting

6.2.1 Study Population

This study aims to include approximately 10 adults treated with maribavir for a refractory CMV infection and who have comorbid ESRD or severe chronic renal disease requiring peritoneal dialysis or hemodialysis. The current study involves a review of routine clinical information available in the medical charts of eligible patients before the study start.

To ensure representation of several European regions, and based on maribavir launch and market uptake, the proposed study countries may include Austria, Belgium, Denmark, Estonia, France, Germany, Italy, Spain, and United Kingdom.

6.2.2 Inclusion Criteria

Eligible patients must have the following attributes documented in the medical record at the time of enrolment to be included in the study:

- Adults ≥18 years of age at index date
- Diagnosis of ESRD or severe chronic renal disease prior to the index date
  - If ESRD: patient diagnosed with ESRD confirmed by an eGFR <15 mL/min
  - If severe chronic renal disease: patient diagnosed with severe chronic renal disease requiring peritoneal dialysis or hemodialysis; patient has an eGFR of 15 to <30 mL/min at index
- Patient has undergone SOT or HSCT before index date
- Patient was diagnosed with refractory (with or without resistance) CMV during the latest post-transplant period
- Patient initiated treatment with maribavir in routine practice within the eligibility period and received at least 1 dose of maribavir
- Informed consent provided (where required by local regulations) before data collection commences

6.2.3 Exclusion Criteria

There are no exclusion criteria for this study

6.3 Data Sources

The primary source for this retrospective study will be the electronic and/or paper medical records of eligible patients included in the study. Site personnel will collect patient data from the records and enter them in a web-based electronic case report form (eCRF) hosted on an electronic data capture (EDC) platform. The eCRF will be accessible via a standard web browser. Study variables to be collected are summarized in Section 6.3.

6.4 Variables

All data collected in the study will be transferred into variables. Completeness of all variables may be dependent on country-specific data privacy regulations (eg, ethnicity/race). Detailed definitions of additional variables that may be derived from the collected data for the statistical analysis will be included in a separate statistical analysis plan (SAP).

The following variables will be collected at the pre-index, index, and post index periods subject to availability in the medical charts. The exposure variables capture the maribavir treatment regimen and the outcome variables capture all safety data. All other variables from this study will be presented by time period.

Current CMV infection and current transplant refer to the latest CMV infection and transplant for which the maribavir treatment was initiated.

6.4.1 Exposure

Maribavir treatment regimen will be captured at index and during the post index period.

Maribavir treatment initiation (at index)

- Start date of treatment
- Daily dose at treatment initiation

Changes in maribavir treatment regimen (post index)

- Changes in the treatment regimen
  - Date of change
  - New daily dose
  - Reason for changes
- Treatment completion or discontinuation
  - Date of completion
  - Date of discontinuation
  - Reason of discontinuation
    - AE/serious AE
    - Lack of efficacy
    - Patient decision
    - Physician decision
    - Death
    - Other

6.4.2 Variables to Address Study Outcomes

Safety data will be collected during the index and post index period, including days after the completion of maribavir treatment or treatment discontinuation. The primary outcome is the incidence of AEs. The secondary outcome is the incidence of AESIs.

AEs

- AE description
  - AESI
    - Immunosuppressant drug concentration level increased
    - Tissue-invasive CMV disease
    - Relapse or progression of the underlying disease for which the transplant was performed
    - Taste disturbance (dysgeusia)
    - Nausea
    - Vomiting
    - Diarrhea
    - Invasive fungal or bacterial infections
    - GVHD
- Start/end dates
- Serious AE/nonserious AE
- AE severity
  - Mild

    - Moderate
    - Severe
- Outcome of AE
    - Fatal
    - Not recovered/not resolved
    - Recovered/resolved
    - Recovered/resolved with sequalae
    - Recovering/resolving
    - Unknown
- Relatedness to maribavir
    - Related
    - Not Related

6.4.3 Pre Index

Medical history

- Chronic kidney disease history
    - Date of diagnosis of chronic kidney disease
- ESRD characteristics
    - Date of ESRD diagnosis
    - Etiology of ESRD
    - eGFR at ESRD diagnosis
- Dialysis history
    - Type
        - Peritoneal
        - Hemodialysis
    - Start/end dates of dialysis
- CMV infection history
    - Date of onset of infection/diagnosis
    - Refractory characteristics
        - Antiviral agent to which CMV infection is refractory
        - Type of drug-resistant mutations (if applicable)
    - Classification of CMV infection
        - Asymptomatic
        - Tissue-invasive CMV disease
        - CMV syndrome
    - Prior anti-CMV prophylaxis and treatment
        - Description of prophylaxis/treatment
        - Start/end dates
        - AEs including renal toxicity from prior anti-CMV treatment
- Transplant history
    - Number of transplants prior to the current transplant
    - Date of transplant(s)
    - Type of transplant(s)
        - HSCT
            - Autologous

- Allogeneic

- SOT
  - Heart transplant
  - Lung transplant
  - Liver transplant
  - Pancreas transplant
  - Intestine transplant
  - Kidney transplant
  - Other transplant

- Reason for transplant(s) (underlying disease)
  - Leukemia (acute myeloid)
  - Leukemia (chronic myeloid)
  - Leukemia (acute lymphocytic)
  - Lymphoma (non-Hodgkin's)
  - Myelodysplastic syndrome
  - Other myeloid malignancy
  - Other
- Stem cell source (for HSCT)
  - Bone marrow
  - Peripheral blood stem cell
  - Cord blood
  - Other
- CMV serostatus of donor and recipient at each transplant
  - Donor positive/recipient positive
  - Donor negative/recipient positive
  - Donor positive/recipient negative
  - Donor negative/recipient negative

6.4.4 Index

Patient demographics

- Year of birth
- Sex
- Ethnicity/race
  - Asian
  - Black
  - Hispanic
  - White
- Age at maribavir treatment initiation

Disease characteristics (at index)

- Current chronic kidney disease status
  - eGFR
  - Chronic kidney disease stages
  - Dialysis status (type, start date)

- Current CMV infection
  - Date of onset of infection/diagnosis
  - Refractory characteristics
    - Antiviral agent to which CMV infection is refractory
    - Type of drug-resistant mutations (if applicable)
  - Agent that patient is refractory to
  - Classification of CMV infection
    - Asymptomatic
    - Tissue-invasive CMV disease
    - CMV syndrome
  - Prior anti-CMV medication used to treat the current CMV infection
    - Induction and maintenance therapy received for transplant, rejection treatment, and other adjuvant/related therapy
    - Start/end dates
    - Other anti-CMV prophylaxis and treatment
    - Other anti-infective agents
  - AEs including renal toxicity from prior anti-CMV treatment
- Current transplant status
  - Date of transplant
  - Type of transplant
    - HSCT
      - Autologous
      - Allogeneic
    - SOT
      - Heart transplant
      - Lung transplant
      - Liver transplant
      - Pancreas transplant
      - Intestine transplant
      - Kidney transplant
      - Other transplant
  - Reason for transplant
    - Leukemia (acute myeloid)
    - Leukemia (chronic myeloid)
    - Leukemia (acute lymphocytic)
    - Lymphoma (non-Hodgkin's)
    - Myelodysplastic syndrome
    - Other myeloid malignancy
    - Other
  - Stem cell source (for HSCT)
    - Bone marrow
    - Peripheral blood stem cell
    - Cord blood
    - Other

    - CMV serostatus
        - Donor positive/recipient positive
        - Donor negative/recipient positive
        - Donor positive/recipient negative
        - Donor negative/recipient negative
- Current GVHD status (for HSCT patients only)
    - Acute GVHD status
        - Presence
        - Absence
        - Grade
    - Chronic GVHD status
        - Presence
        - Absence
        - Grade
- Relevant comorbidities ongoing or diagnosed at index date and treatment

Concomitant medications ongoing or starting at index date

- Drug name
- Start/end dates

6.4.5 Post index

CMV status

- Resolved
    - Date of resolution
- Unresolved

Concomitant medications

- Drug name
- Start/end dates

Dialysis treatment during maribavir treatment

- Type and frequency
- Changes in dialysis treatment
  Reason for change

Patient status

- Death
    - Date of death
    - Primary cause of death
- Lost to follow-up
    - Date of loss to follow-up

6.5 Study Size

The source population for the current PASS comprises of post-transplant patients with CMV infection/disease refractory (with or without resistance) to prior antiviral treatments and a post-transplant diagnosis of comorbid ESRD or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis. As such, study size will be dependent on the patterns of use of maribavir in routine clinical practice during the first years after launch for an indication that is expected to be ultra rare.

Considering the eligibility criteria, coupled with the rarity of the source population, the target sample size for this PASS is approximately 10 patients. This target sample size was determined by practical and feasibility assessments, and findings from the pivotal SHP620-303 (SOLSTICE) trial. Of the 352 randomized patients in the SOLSTICE trial, only 11 patients with 8 (2.3%) on maribavir treatment had severe chronic renal disease, defined as creatinine clearance <30 mL/minute according to the Cockcroft-Gault formula (Avery et al. 2022; Sampson and Drury 1992). Notably, patients in the SOLSTICE trial were not on dialysis; the current study aims to further select patients from an already rare population. Although no formal hypotheses have been prespecified and sample size calculations are not applicable, best estimates and 95% confidence intervals (CIs) for various sample sizes are presented in Table 3.

Table 3 Best Estimate and 95% CIs for a Population Proportion According to Expected Patient Counts for Different Possible AE Rates

% of Participants with AEs	Sample Size	
	10	20
5%	38.1% (0%, 38.1%)	24.7% (0.1%, 24.9%)
20%	53.1% (2.5%, 55.6%)	37.9% (5.7%, 43.7%)
35%	60.4% (9.3%, 69.6%)	43.8% (15.4%, 59.2%)
50%	62.6% (18.7%, 81.3%)	45.6% (27.2%, 72.8%)
65%	60.4% (30.4%, 90.7%)	43.8% (40.8%, 84.6%)
80%	53.1% (44.4%, 97.5%)	37.9% (56.3%, 94.3%)
95%	38.1% (61.9%, 100%)	24.7% (75.1%, 99.9%)

6.6 Data Management

Data management will be conducted in accordance with the data management plan. This plan will be developed and approved before finalizing the design of the study database that provides data collection tools to the site. The data management plan will address processes, responsibilities, and resources for data handling during the study and after completion; types of data and data sources; ethics; storage, back up and security; and data sharing/data use agreements.

The sponsor will provide a password-protected, web-based EDC system to serve as an integrated, transparent tool to collect and manage data and track study progress at the center and patient level. Data in the EDC system will be kept in a central location, and all data will be transmitted to a central database.

For the chart review, information from patient medical records will be collected by study sites and entered directly into the eCRF. There will be 2 waves of data extraction, during which the sites will be invited to perform data extraction of eligible patients into the eCRF. Prior to the start of data extraction, sites will be fully trained to use the online EDC system and will receive eCRF completion guidelines. Sites will be responsible for entering abstracted patient data into a secure, internet-based EDC study database via the eCRF. Investigators and authorized site personnel will be able to access their account with a username and password. All eCRFs should be completed by the investigator, study coordinator, or designated trained personnel, as appropriate. All changes or corrections to the eCRFs will be documented in an audit trail and an adequate explanation will be required.

The EDC system will include logic checks to minimize data entry errors. Data inconsistencies outside the logic checks will be managed by manual queries issued by data management within the EDC system for site completion. All queries will be monitored until there is a resolution within the EDC through the electronic query report.

After all study data are abstracted and reviewed, in accordance with the data management plan, the database will be locked and transferred to the sponsor or designate. Takeda will file a validated copy of the study database after database lock.

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records [eg, eCRFs and medical records]), source documents, detailed records of patient disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone calls/reports). The records should be retained by the investigator for the length of time specified in local regulations or in the site contract agreement (whichever time period is longer).

If the investigator is not available (eg, retirement or relocation) to continue to retain the study records for the required period, the sponsor should be notified. The study records must be transferred to a designee approved by the sponsor, such as another investigator, another institution, or an independent third party arranged by the sponsor. The investigator must obtain the sponsor's written permission before disposing of any records, even if retention requirements have been met.

6.6.1 Data Collection Tool

The sponsor will provide a web-based EDC system (Medidata RAVE system) to serve as an integrated, secure, transparent, and validated tool to collect and manage data and track study progress at the site and patient level. Data in the EDC system will be kept in a central location and all data will be transmitted to a central database.

The EDC system will meet approved and established standards for the security of health information, be validated, and be 21 Code of Federal Regulations Part 11 compliant. To ensure that patient data (as well as other confidential data) remain secure and intact, standard operating procedures and quality control processes that address patient data security will be followed. The EDC system will have built-in edit checks and validations and will support electronically generated and manual queries.

The study site investigator must provide a signature to confirm the collected data.

6.6.2 Data Flow

The data flow for this chart review study is summarized below:

- The source for data collected will be patient medical records (electronic and/or paper charts) that are stored at the site.
- Site staff will be trained by the contract research organization (CRO) to perform the chart abstraction, including data entry and how to retrieve and respond to data queries in the EDC system. It is assumed that all sites will be able to complete data entry into the eCRFs via the EDC system.
- The EDC system will include logic checks to minimize data entry errors. Data inconsistencies outside the logic checks will be managed by manual queries issued by data management within the EDC system for site completion. All queries will be monitored until resolution within the EDC through the electronic query report.
- Each study investigator has the ultimate responsibility for the collection and reporting of all data entered in the eCRFs and any other data collection forms (source documents), and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be signed before database lock by the study investigator attest that the data contained are correctly recorded.
- The data entered into the EDC system will contribute to a custom study database for the purpose of analysis in this study.

6.7 Data Analysis

The statistical analysis of the data will be primarily descriptive, without prespecified hypotheses, but inferential statistics will be used to estimate the precision around descriptive estimates (eg, 95% CI), if the sample size allows. The final analyses will be performed once the data from all patients has been collected in the database, cleaned, and database lock has occurred. Post hoc analyses may be completed to support planned study analyses, and these will be clearly identified as such in the clinical study report.

Full details on data transformations/derivations, categorical definitions, subgroup analyses, handling of missing data and censoring, and presentation of results will be described separately in the SAP, which will be developed and finalized before any planned analysis. The final SAP will include table shells to be populated during the analyses.

For purposes of the summary tabulations, patient data will be pooled across all study sites. Stratifications by country are not foreseen. In general, data summaries will be presented overall and by the subgroups of interest where applicable.

Demographic and baseline characteristics will be summarized using descriptive statistics.

Medical Dictionary for Regulatory Activities (MedDRA) coding version 25.0 or later will be used to classify and tabulate AEs/adverse drug reactions (ADR). Frequencies (absolute and percentages) across system organ class (SOC), for individual events within those classes and preferred terms (PT), will be provided and calculated with 95% CIs.

All statistical analyses will be performed using SAS version 9.4 or higher or SAS Enterprise Guide version 7.1 or later (SAS Institute, Cary, NC 27513).

6.7.1 Statistical Methods

Unless otherwise specified, all statistical analyses will be descriptive in nature. Continuous variables will be described by the number of eligible participants and missing data, mean, standard deviation, median, first quartile, third quartile, and minimum and maximum values. Categorical variables will be described as the total number of participants and relative percentage per category. Percentages will be calculated using the most appropriate denominator. Two-sided 95% CIs will be reported as appropriate.

Should missing data occur, missing data will not be imputed and the data will be analyzed as they are recorded in the study eCRFs. However, for all missing dates, some date imputation may be performed. The general imputation rules will be described in the SAP. Missing data may be included as a separate category in some cases, depending on the nature of the variable. Unless otherwise specified in a table's footnote, missing values will not be included in the denominator for summarizing a categorical variable's distribution. If the eCRF includes a selection of "unknown," these responses will not be considered missing responses and will be included in the distributions.

Descriptive analysis will be performed on the variables listed in Section 6.4. Year of birth will be analyzed as age and age group, and dates would be as duration or index days/weeks. Detailed definitions of additional variables that may be derived from the collected data for the statistical analysis will be included in a separate SAP.

Incidence of each outcome will be expressed per person-year of exposure to account for varying length of follow-up. Incidence rates will be calculated as the number of patients with an event of interest, divided by the number of person-years at risk, ie, the summed person-year of maribavir exposure. Only new cases will be included in the numerator; patients with existing AEs at the index date who reported the AE before the index date will not be counted, and patients who initially experience AEs at index or at the post index date will be counted only once in the numerator (ie, worsening outcomes will not be counted as new cases). The following definitions will be used to estimate incidence rates:

- Person-days at risk for an individual will be defined as the total number of days of maribavir exposure (ending at the date of the outcome of interest, the final dose of maribavir +7 days, death, or end of data availability). For each incidence rate, 95% CIs will be calculated using exact methods.
- The follow-up period (person-days) will be defined as the period from the index date until the earliest of: 7 days following the date of discontinuation of initiated maribavir medication, end of data availability, or death.
- Person-years will be calculated by dividing person-days by 365.

6.7.1.1 Primary Objective

Incidence rates (number of first events per person-year at risk) of AEs and ADRs (overall, and by SOC and PT) after administration of maribavir over the follow-up period will be computed along with 95% CIs. The number and percentage of patients with AEs and ADR, total number of AE and ADR, and AEs and ADR rate (total number of each event per person-year) will also be summarized.

The distribution of AEs by severity, seriousness, outcome, and physician's causal assessment will be tabulated.

Analyses will be based on the evaluable safety population, defined as patients who receive at least 1 dose of maribavir.

Subgroup analyses may be performed by select baseline characteristics, treatment conditions, and any other variables of interests. Subgroup analyses may be identified post hoc during analysis.

Listings of individual participants data of the AEs and serious AEs, as well as the narrative statements of events, will be reported.

6.7.1.2 Secondary Objective

Incidence rates (number of first events per person-year at risk) of each AESI after administration of maribavir over the follow-up period will be computed along with 95% CI. The number and percentage of patients with each AESI, total number of each AESI, and AESI rate (total number of each event per person-year) will also be summarized.

The distribution of AESI by severity, toxicity, seriousness, and physician's causal assessment will be tabulated.

Listings of individual participants data of the AESIs, as well as the narrative statements of events, will be reported.

6.8 Quality Control

The CRO will perform site monitoring through a hybrid approach for data quality, compliance, and timely data collection in accordance with the monitoring plan. Alternative approaches, such as remote source data verification, may be used to ensure data quality and integrity as well as maintain patient safety where allowed by local laws and regulations. During the study, the site investigator will be required to maintain a study site file that will include the following essential documents and other documents as specified in the monitoring plan:

- Written agreement between the sponsor and study site
- Study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements
- List of participating patients
- Written IRB or EC approval and vote, according to local regulations
- Authority approval according to local regulations
- Patient information sheet and/or informed consent form in local language, approved by IRBs or ECs, including the original signed forms, as required. An exemption or waiver of informed consent will be sought from all relevant IRBs or ECs; this item applies to sites that do not receive approval of the waiver.

6.8.1 Data Validation

Data collection procedures will be reviewed with site personnel during site initiation. Data will be validated at the point of entry through the EDC platform using soft and hard stops to maximize the degree of clean and complete data when published to the database.

Plausible value ranges for numerical data, logical data, and list entries will be filed in the eCRF. Tests for consistency and completeness based on these conditions will be performed during data entry in the eCRF. The validity of the recorded data will therefore be ensured by the validations incorporated in the documentation system, which highlight incorrect or implausible entries to the individual entering the data.

Edit checks include data type (integer, decimal, text), range, length (maximum characters or number length), precision (decimal places), date ranges, missing data in required fields, and overlapping data. In addition, data can be compared against absolute values (eg, study start), values on the same screen, values in other data entry sessions, calculated (dynamic) values, and multiple values. Corrections made after the data are saved will be documented in an audit trail.

The clinical data manager will review data issues raised by online and post-entry checks using validation programs and data listings. Since all data will be collected retrospectively, most queries will address data entry errors. Information that is not in the medical record will not be queried.

If clarifications are needed, data queries will be created through the web-based application. Site personnel will be required to respond to the queries and correct the study database, if needed. The site investigator will retain full responsibility for the accuracy and authenticity of all eCRF data. Additional details will be delineated in the data management plan.

6.8.2 Archiving of Study Documentation

The site investigator must maintain adequate and accurate records to enable verification of the study process and data. After final database lock, the site investigator will be required to store the list of participating patients, signed informed consent forms (as applicable), and other documents delineated during site initiation onsite for 5 years. After that period, the documents may be destroyed or retained as required by local regulations and site requirements. Takeda must be notified in advance if the site investigator plans to assign the study records to another party or move them to another location. Following study completion, a complete copy of the study data will be provided to Takeda for archival purposes.

6.8.3 Audits and Inspections

The sponsor's quality assurance unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that the study data are correct and complete. Representatives from IRBs, ECs, or competent authority may, in rare cases, wish to inspect the study on site. Upon receiving notification of such inspection, the site investigator must immediately contact the sponsor and make the records available as requested.

6.9 Limitations of the Research Methods

Due to the rare occurrence of the population of interest, a small sample size is projected that limits the precision of estimates. To maximize the sample size, the study will aim to include all available and eligible patients at the site rather than limiting enrolment by site or country.

Several factors may impact the sample size, notably maribavir market launch and uptake in the different European countries. Monitoring of patient inclusion at the site and country levels will allow the deployment of mitigation strategies in response to any challenges. Such plans will be discussed by the marketing authorization holder and the Pharmacovigilance Risk Assessment Committee. They may include the initiation of additional sites within the participating countries and/or expanding the study into other countries.

Given the retrospective nature of this study, data quality and completeness will be dependent on the quality, eg, accuracy and comprehensiveness, of the information reported in the medical records and the accuracy and consistency of data entry in the eCRF by investigators. In addition, availability of information in records may vary by physician practice and will reflect differences in practice patterns, recording practices, and medical norms. The eCRF will be designed to minimize the level of missing data collected. Additionally, data collectors will be given detailed guidance for accurate completion of the eCRF. Remote central monitoring will be conducted promptly after data entry so that queries can be raised in a timely manner. In addition, the EDC system includes edit checks designed to deliver data that is predominantly clean upon data entry. Missing exposure and outcome dates in the medical record will not be imputed to avoid information bias.

As with all observational studies, one of the greatest concerns for external validity is selection bias. In order to minimize this source of bias, physicians will be instructed to include consecutive eligible patients to limit the risk of physician's inclination to include only their "best" patients in the study.

Selection bias will be mitigated by the consecutive inclusion of patients. Physicians will be asked to include all eligible patients until the sample size is reached. Selection bias due to non-consent will be mitigated by the inclusion of deceased patients, for which no informed consent is required (except in Austria and Germany). In countries where informed consent for patients is required, selection bias will be mitigated by providing clear information to patients on the importance of the study and the absence of burden for them. The extent of the selection bias will be monitored via the maintenance of a screening log at the site.

Participation in the study is dependent on physicians' ability and willingness to participate. Hence, there is a possibility that included physicians are not fully representative of the complete targeted physician population, which could impact patient representativeness.

7. PROTECTION OF HUMAN SUBJECTS

The study is a PASS and as such will comply with the definition of the noninterventional (observational) study provided in the Guideline on Good Pharmacovigilance Practices: Module VIII – Post Authorization Safety Studies (reference from EMA).

This study will be conducted in accordance with the current version of the Declaration of Helsinki (World Medical Association 2013), the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) (reference from ISPE), and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (reference from ENCePP). The ENCePP Checklist for Study Protocols (encepp.eu/standards_and_guidances/checkListProtocols.shtml, ENCePP Checklist for Study Protocols, Accessed 22 March 2023) will be completed (Appendix B), and the study will be registered in the European Union electronic register of post authorization studies (encepp.eu/encepp_studies/indexRegister.shtml, The European Union electronic Register of Post-Authorisation Studies (EU PAS Register), Accessed 22 March 2023). Additionally, the study will adhere to local regulations and the General Data Protection Regulation (2016/679) (reference from the European Parliament and the Council of European Union).

The study does not impact the day-to-day life of the participating patient. This retrospective, observational, noninterventional study is based on the collection of existing data from patients' medical records previously collected for routine clinical care and not for research purposes. There are no study visits, procedures, interventions, or prospective data collection. Therefore, it is unlikely that this study would adversely affect the rights and welfare of the patients, increase their risk for harm, or impact on their medical care.

In a retrospective medical record review study with reasonable and appropriate data protections, risks related to a breach of confidentiality are minimal. In this study, the risk is minimized in the following ways. The patient's identity will only be known to the participating sites and site investigators. All medical record data will be processed in a fully confidential manner. No identifiable/contact information will be collected from patients' records for the study. All patient-level data will be pseudonymized and assigned a unique ID, which will be generated by the eCRF system. The eCRF will not collect any personal or identifiable information.

7.1 Informed Consent

All medical record data will be abstracted retrospectively; therefore, an exemption or waiver of informed consent will be sought from all associated IRBs and ECs for deceased patients. A waiver of informed consent may also be sought for alive patients, but it is expected that this is not allowed in most European countries. Where informed consent is required, it will be collected from patients by the site investigators in accordance with local ethical and institutional requirements. If required, as part of the informed consent, the patient must agree that sponsor personnel or their representatives or IRB/EC or competent authority personnel (national or other) may require direct access to their medical records from which data will be collected, processed, and stored in a pseudonymous form for evaluation of this study and any later overviews. Data

may also be transferred in pseudonymous form to third parties, eg, to other companies or authorities, that may be located in other countries.

7.2 Ethical Review

Full ethical approval will be sought with relevant IRBs/ECs and/or any other required reviews of the study protocol by specific committees will be obtained in accordance with applicable national and local regulations. The study will adhere to the local regulations and decisions of the IRBs or ECs from the participating sites and countries. According to applicable regulations, the sponsor, appointed CRO, or site investigator will obtain approval of the protocol and associated documents from the relevant IRBs or ECs. Other required documentation such as periodic updates on the progress of the study, notification of the end-of-study, and summary of the study results will be submitted to the IRB or EC. The sponsor or the appointed CRO will send required documents to the competent authority and/or other national or regional authorities. The sponsor or the appointed CRO will keep an updated list of submission and approval dates and a copy of all documents submitted.

8. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Events

An AE is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for a serious AE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the healthcare provider considers to be clinically significant

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrences that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the healthcare provider, places the subject/patient at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- An SAE may also be other medically important events that, in the opinion of the health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

8.1.3 Adverse Drug Reactions

An ADR is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

8.1.4 Product Quality Complaints

A product quality complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, strength, purity, effectiveness, or performance of a product or device and combination product after it is released for distribution.

8.1.5 Special Situation Reports

A special situation report includes any of the following events:

- Pregnancy: any case in which a pregnancy patient is exposed to a Takeda product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: infant exposure from breast milk.
- Overdose: all information of any accidental or intentional overdose.
- Drug abuse, misuse, or medication error: all information on medicinal product abuse, misuse, or medication error (potential or actual).
- Suspected transmission of an infectious agent: suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda product.
- Accidental/occupational exposure.
- Use outside the terms of the marketing authorization, also known as “off-label”.
- Use of falsified medicinal product.
- Use of counterfeit medicinal product.
- Drug-drug interactions and drug-food interactions.
- Inadvertent or accidental exposure with or without an AE.
- Unintended benefit.

A special situation report should be prepared even if there is no associated AE.

8.2 Collection and Notifying of Adverse Events, Special Situation Reports, and Product Quality Complaints

SAEs, AEs, ADRs, special situation report, and product quality complaints in the medical chart records or other applicable source data that are part of the study objectives or endpoints

Events/complaints which are part of the study objectives or endpoints will be systematically identified and collected from medical chart records or other applicable source records and summarized as part of any interim analysis, if applicable, and in the final study report. Such events do not need to be notified as individual reports to Takeda Pharmacovigilance.

SAEs, AEs, special situation report, and product quality complaints in the medical chart records or other applicable source data that are not part of the study objectives and endpoints

Events/complaints that are not part of the study objectives and endpoints will not be abstracted or collected from medical chart records or other applicable source records.

SAEs, AEs, ADRs, special situation report, and product quality complaints spontaneously reported to the investigator(s) or research team

If during the conduct of the study, the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, special situation report or product quality complaint, where the event/complaints pertains to a Takeda product (or unbranded generic), such information should be forwarded to the relevant Takeda departments via email within one working day for fatal or life-threatening SAEs, within four calendar days for other SAEs, and within seven calendar days for all other events. This includes events spontaneously notified to the investigator(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any AEs should be assumed unless there is evidence to the contrary.

SAE, AE, ADR and special situation report information should be forwarded to GPSE@takeda.com, and product quality complaints should be forwarded to pqc@takeda.com.

9. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The sponsor will ensure that study results are made publicly available as required by local authorities. The sponsor may post the results of the study on the European Union Post Authorization Study Register, ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws, and regulations. The final study report will be available to regulatory authorities as described in Section 3. Site investigators will be informed about the results when the report is finalized. The sponsor will adhere to regulatory reporting requirements as specified in official communications.

The sponsor has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners. Published study results will follow recommendations of the International Committee of Medical Journal Editors (icmje.org/recommendations/, Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals, Accessed 22 March 2023). Communication in appropriate scientific venues will be considered. When reporting the results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed (von Elm et al. 2014).

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Appendix A LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Not available yet	To be developed	Data Management Plan
2	Not available yet	To be developed	Statistical Analysis Plan

Appendix B ENCEPP CHECKLIST

Doc.Ref. EMA/540136/2009
Adopted by the ENCePP Steering Group on 15 Oct 2018

ENCePP Checklist for Study Protocols (Revision 4)

Study title: Retrospective chart review of safety outcomes associated with use of maribavir in patients with post-transplant refractory cytomegalovirus (CMV) infection and comorbid end-stage renal disease (ESRD) or comorbid severe chronic renal disease requiring peritoneal dialysis or hemodialysis.

EU PAS Register® number: Study will be registered in EU Post Authorization Study (PAS) Register following Pharmacovigilance Risk Assessment Committee (PRAC) approval of final protocol and before study initiation.

Study reference number (if applicable): Not applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	9
1.1.2 End of data collection[2]	☒	☐	☐	9
1.1.3 Progress report(s)	☒	☐	☐	9
1.1.4 Interim report(s)	☐	☐	☒	NA
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	9
1.1.6 Final report of study results	☒	☐	☐	9

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	11
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	10
2.1.2 The objective(s) of the study?	☒	☐	☐	11
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	10
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	NA
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	NA

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	12.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	12.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	12.7.1
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	NA
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	14

Comments:

Measures of association are not included in this single cohort design (no comparator group).

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	12.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	12.1
	4.2.2 Age and sex	☒	☐	☐	12.2.2
	4.2.3 Country of origin	☒	☐	☐	12.2.1
	4.2.4 Disease/indication	☒	☐	☐	12.2.2
	4.2.5 Duration of follow-up	☒	☐	☐	12.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	12.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	12.3, 12.7.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure categorized according to time windows?	☒	☐	☐	12.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	12.3, 12.7.1
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	10
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	12.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	12.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	NA
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	NA
7.2	Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	12.9
7.3	Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	12.9

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	12.7.1.1

Comments:

Subgroup analyses may be performed by select baseline characteristics, treatment conditions, and any other variables of interests. Subgroup analyses may be identified post hoc during analysis.

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	12.4
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	12.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	12.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	12.3.1
	9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	12.3.2
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	12.3.3, 12.3.4, 12.3.5
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	NA
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	12.7
	9.3.3 Covariates and other characteristics?	☐	☐	☒	NA
9.4	Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☐	☒	☐	

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	12.7.1
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	12.5
10.3	Are descriptive analyses included?	☒	☐	☐	12.7.1
10.4	Are stratified analyses included?	☒	☐	☐	12.7.2
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	12.7.2
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	12.7.1
10.8	Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	12.6
11.2	Are methods of quality assurance described?	☒	☐	☐	12.8.3
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	12.8.3

Comments:

Section 12: Limitations		**Yes**	**No**	**N/A**	**Section Number**
12.1	Does the protocol discuss the impact on the study results of:				
	12.1.1 Selection bias?	☒	☐	☐	12.9
	12.1.2 Information bias?	☒	☐	☐	12.9
	12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2	Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	12.5, 12.9

Comments:

Section 13: Ethical/data protection issues		**Yes**	**No**	**N/A**	**Section Number**
13.1	Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13.2
13.2	Has any outcome of an ethical review procedure been addressed?*	☒	☐	☐	13.2
13.3	Have data protection requirements been described?	☒	☐	☐	12.6.1

Comments:

*An exemption or waiver of informed consent will be sought from all relevant IECs or IRBs

Section 14: Amendments and deviations		**Yes**	**No**	**N/A**	**Section Number**
14.1	Does the protocol include a section to document amendments and deviations?	☒	☐	☐	8

Comments:

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Section Number**
15.1	Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	15
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	15

Comments:

Name of the main author of the protocol: [redacted]

Date: 06-Jun-2023 | 12:15:47 EDT

Signature: DocuSigned by: [redacted]