EU RISK MANAGEMENT PLAN (RMP)

for

LIVTENCITY™ (Maribavir)

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List of Abbreviations

Abbreviation	Definition/Description
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
AST	Aspartate Aminotransferase
AST	Alanine Aminotransferase
ATC	The Anatomical Therapeutic Chemical Classification
AUC	Area Under the Curve
BCRP	Breast Cancer Resistant Protein
CI	Confidence Interval
CMV	Cytomegalovirus
CNS	Central Nervous System
CV	Cardiovascular
DDI	Drug-Drug interaction
DNA	Deoxyribonucleic Acid
EEA	European Economic Area
eGFR	estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
EU	European Union
GI	Gastrointestinal
GVHD	Graft-Versus-Host Disease
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSCT	Hematopoietic stem-cell transplantation
INN	International Nonproprietary Names
ISDLI	Immunosuppressant Drug Level Increased
MDRD	Modification of Diet in Renal Disease

Abbreviation	Definition/Description
NOAEL	No Observed Adverse Effect Level
OAT	Organic Anion Transporter
OATP	Organic Anion Transporting Polypeptide
OCT	Organic Cation Transporter
P-gp	P-Glycoprotein
PI	Product Information
QPPV	Qualified Person Responsible For Pharmacovigilance
RMP	Risk Management Plan
RNA	Ribonucleic acid
SOT	Solid Organ Transplantation
TEAE	Treatment-Emergent Adverse Event
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal

Part I: Product Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Maribavir
Pharmacotherapeutic group(s) (ATC Code)	Pharmacotherapeutic group = Antivirals for systemic use, direct acting antivirals; ATC code = J05AX10.
Marketing Authorisation Applicant	Takeda Pharmaceuticals International AG Ireland Branch
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	LIVTENCITY
Marketing authorisation procedure	Centralised.
Brief description of the product	Chemical class: Benzimidazole ribosides
	Summary of mode of action: Maribavir is a potent and selective, orally bioavailable antiviral drug with a novel mechanism of action against human CMV. Maribavir attaches to the UL97 encoded kinase at the adenosine triphosphate binding site, abolishing phosphotransferase needed in processes such as DNA replication, encapsidation, and nuclear egress.
	Important information about its composition: Maribavir drug product is provided as an immediate release film-coated tablet for oral administration, available in a single strength of 200 mg of maribavir. The maribavir 200 mg film-coated tablet is a blue, oval-shaped, convex tablet, de-bossed with 'SHP' on one side and '620' on the other side. The inactive ingredients are microcrystalline cellulose, sodium starch glycolate, magnesium stearate and blue Opadry II film coating.
Hyperlink to the Product Information (PI)	<Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.>
Indication(s) in the EEA	Current: Treatment of cytomegalovirus (CMV) infection and/or disease that is refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or

	foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT). Consideration should be given to official guidance on the appropriate use of antiviral agents
Dosage in the EEA	Current: The recommended dose of LIVTENCITY is 400 mg (two 200 mg tablets) twice daily resulting in a daily dose of 800 mg for 8 weeks. Treatment duration may need to be individualised based on the clinical characteristics of each patient.
Pharmaceutical form(s) and strengths	Current: Film-coated 200 mg tablet for oral use.
Is/will the product be subject to additional monitoring in the EU?	Yes.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Cytomegalovirus infection or disease in adult transplant patients who are resistant or refractory to prior therapy

Incidence in transplant recipients:

Estimates of CMV infection and disease in European countries indicate that in solid organ transplant (SOT) recipients, CMV infection occurs in up to 46.5% (France) and CMV disease can occur in up to 16.0% (Spain). Following Hematopoietic stem-cell transplantation (HSCT) in Spain the incidence of CMV infection and disease has been observed in up to 53.8% and 4.8% transplant recipients, respectively. A summary of European estimates of CMV incidence and disease based on recent publications is presented below:

Table 1: Estimated Incidence Rates of CMV Infection and CMV Disease following SOT and allogeneic HSCT in European countries based on published studies

Transplantation	CMV Infection	CMV Disease
SOT	22.9% (Denmark) to 46.5% (France) [1-13]	5.5% (Denmark) to 16.0% (Spain) [1-4,6,9,10,14-16]
HSCT	29.0% (Germany) to 53.8% (Spain)[13,17-23]	2.8% (Spain) to 4.8% (Italy)[18,22]

Prevalence in general population:

Cytomegalovirus is a ubiquitous beta herpesvirus that commonly infects humans. Primary infection with CMV is typically asymptomatic [24]. Serologic evidence of prior infection can be found in 40-100% of various adult populations [25]. Assays of donor blood samples drawn from 313 healthy volunteers with no medical history of CMV infection for presence of CMV antibodies and CMV Ribonucleic acid (RNA) detected CMV antibodies in 117 (37%) of the samples, and CMV-specific RNA was detected in 136 (43%) of samples. Of the 196 samples negative for CMV antibodies, 44% tested positive for CMV RNA [26].

Demographics of the target population in the proposed indication:

Annually, approximately 45,000 SOTs [27] and 19,000 allogeneic stem-cell transplants [28] are performed across Europe. Following a transplantation, CMV infection can result from the transmission of CMV virions from donor tissue, or from reactivation of a latent CMV infection in the transplant recipient. The risk of CMV infection is influenced by a number of factors such as the CMV serostatus of the donor and recipient, the type of organ transplanted, the net state of the host immunosuppression, and viral factors. Both directly and indirectly, CMV infection is the leading viral cause of morbidity and mortality amongst SOT recipients [29]. Graft loss is a known significant and indirect effect of CMV disease in SOT

Cytomegalovirus infection or disease in adult transplant patients who are resistant or refractory to prior therapy	
	recipients and can occur in 7.9% SOT recipients with CMV disease [15]. In allogeneic HSCT recipients, patients with CMV infection have approximately 2-fold higher risk of overall mortality [30].
Risk factors for the disease:	Immunocompromised individuals, including those treated with immunosuppressive drugs following HSCT or SOT, have the greatest risk for serious CMV disease. Seropositivity status of the donor and recipient is the main risk factor for invasive CMV disease in both HSCT and SOT. For HSCT, recipients who are seropositive (R+) at the time of transplant are at greatest risk for symptomatic CMV infection. Without prophylaxis, approximately 80% of CMV-seropositive patients experience CMV infection after allogeneic HSCT. Current preventive strategies have decreased the incidence of CMV disease, which had historically occurred in 20% to 35% of these patients [31]. In SOT, seronegative patients who receive seropositive grafts are also at increased risk for primary CMV transmission and clinical disease. In kidney transplant recipients, the highest incidence of symptomatic CMV infection (syndrome) or disease occurs in CMV seronegative recipients who receive a kidney from a CMV-seropositive donor (D+/R-) [32-35]. CMV disease is associated with increased morbidity, mortality, and poor long-term outcomes [36,37]. Allograft rejection is a major risk factor for CMV, especially when patients are treated with lymphocyte-depleting antibodies, and the risk of CMV varies by transplant type with vascularized composite allograft tissue and small intestinal transplant recipients at highest risk among SOT populations [38]. With regards to demographic characteristics including age, sex, and race there are little to no risk factors associated with CMV incidence following SOT and HSCT. Research has indicated that these demographic factors do not play a role in CMV incidence following SOT [39,40]. However, older age may play a role in CMV reactivation following allogenic-HSCT [41,42]. This may be due to the increased prevalence of CMV seropositivity in the general population with increasing age [42,43]. It should be noted that the prevalence of CMV seropositivity in the general population is greater in females and non-whites [43].
The main existing treatment options:	There are limited therapeutic options available to treat CMV infection in the transplant population. Ganciclovir was approved by the European Medicine Agency for the treatment of CMV disease in immunocompromised patients. However, there are no approved therapies to treat CMV infections that are resistant/refractory to prior antiviral therapy. These patients are at highest risk of developing or already have developed serious CMV complications and are left with limited or no viable options. While physicians use a variety of strategies with existing anti-CMV agents to overcome treatment resistance/refractoriness (e.g., increasing dose, decreasing immunosuppression, administering growth factors to combat hematotoxicity, dose reductions to minimise renal toxicity,

Cytomegalovirus infection or disease in adult transplant patients who are resistant or refractory to prior therapy	
	etc.), there are still patients that exhaust treatment options and ultimately lose their graft or die as a result of CMV infection or disease [44-47].
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	Serious HCMV disease occurs almost exclusively in individuals with compromised or immature immune systems, including transplant recipients, patients with acquired immunodeficiency syndrome (AIDS), immunosuppressed cancer patients, and neonates. Disease manifestations include retinitis, colitis, esophagitis, pneumonia, hepatitis, and meningoencephalitis. CMV disease may present as CMV syndrome manifesting as fever, malaise, atypical lymphocytosis, leukopenia or neutropenia, thrombocytopenia, and elevated hepatic transaminases, or as end - organ CMV disease such as gastrointestinal (GI) disease, pneumonitis, hepatitis, nephritis, myocarditis, pancreatitis, encephalitis, retinitis, or other end-organ disease [38]. CMV is more likely to infect the transplanted allograft. Without prophylaxis, CMV disease typically occurs within 3 months following SOT and HSCT. Estimated incidences of early CMV disease (before day 100 post-transplant) and late CMV disease (after day 100) in CMV-seropositive allogeneic recipients are currently around 5% and 15% [48]. Both directly and indirectly, CMV infection is the leading viral cause of morbidity and mortality amongst SOT recipients [29]. Graft loss is a known significant and indirect effect of CMV disease in SOT recipients and can occur in 7.9% SOT recipients with CMV disease [15]. In allogeneic HSCT recipients, patients with CMV infection have approximately 2-fold higher risk of overall mortality [30].
Important co-morbidities:	CMV disease is associated with an increased incidence of opportunistic infections, an association between CMV and graft-versus-host disease (GVHD) predominately in HSCT patients, and associations between CMV and graft rejection or other allograft pathology in SOT patients, and reduced patient survival [49-51]. Such organ-specific associations with CMV include bronchiolitis obliterans in lung recipients, vanishing bile duct syndrome in liver recipients, accelerated transplant vasculopathy in heart recipients and transplant glomerulopathy, transplant renal artery stenosis or increased risk of transplant rejection [52-57]. These effects are believed to be mediated by the virus's ability to modulate the immune system, either directly or secondary to the host antiviral response through regulation of cytokine, chemokine, and/or growth factor production.

Part II: Module SII - Non-clinical part of the safety specification

A comprehensive non-clinical testing program including pharmacodynamics, secondary pharmacology, safety pharmacology, pharmacokinetics (PK), and toxicology has been completed to support oral dosing of maribavir in the treatment of transplant patients with CMV infection or disease resistant or refractory to current CMV agents. For the non-clinical development program rats and cynomolgus monkeys were selected as the primary rodent and nonrodent species, respectively.

The toxicological assessment of maribavir included single-dose oral and intravenous studies in mice and rats, and oral repeat-dose toxicity studies with dosing durations of up to 13 weeks in mice, 26 weeks in Sprague-Dawley rats, and 52 weeks in cynomolgus monkeys.

The genotoxic potential of maribavir was evaluated in-vitro in a bacterial reverse mutation and mouse lymphoma assays, and in vivo in a micronucleus assay in rats, and the carcinogenic potential of maribavir was assessed in lifetime bioassays in mice and rats. To establish the potential for reproductive and/or developmental toxicity, fertility, combined embryo/foetal development, and pre-and postnatal development studies were conducted in rats and/or rabbits, and juvenile toxicity was investigated in rats. Local irritation (eye and dermal) studies in rats, rabbits, and guinea pigs, immunotoxicity assessment in rats and an in-vitro phototoxicity study were also conducted.

Important safety findings from completed non-clinical studies with maribavir are summarised below.

Key Safety Findings	**Relevance to human usage**
Toxicity:	
Single and Repeat-dose toxicity studies	
Mortality was observed following single doses in mice and rats at doses ≥500 mg/kg and ≥ 1000 mg/kg, respectively. In repeat-dose studies, mortality was observed in mice at doses ≥ 300 mg/kg/day (19 males and 18 females), and in rats at 400 mg/kg/day in the chronic 26-week study (1 male and 4 females). In the 52-week monkey study, 2 males at 400/300 mg/kg/day and 1 male at 200 mg/kg/day were euthanised in extremis. In pivotal repeat-dose oral toxicity studies in rats (6 months) and monkeys (12 months), the major findings were reversible regenerative anaemia and histologic change of mucosal cell hyperplasia in the intestinal tract associated with clinical observations of soft to liquid stool, electrolyte changes and dehydration, which were reversible or showed progression to recovery after cessation of dosing. The GI effects were representative of human GI-related adverse events. A no observed adverse effect level (NOAEL) was not established in monkeys and was therefore considered to be <100 mg/kg/day, the lowest dose tested. In rats, the NOAEL was considered to be 25 mg/kg/day. Whilst the NOAELs / lowest-observed-adverse-effect levels were at sub-therapeutic exposures, the	There is a potential for mild to moderate anaemia and/or GI-related events such as diarrhoea.

Key Safety Findings	Relevance to human usage
key toxicities were reversible upon discontinuation of treatment and are clinically monitorable.	
Reproductive and Developmental Toxicity:	
Maribavir did not affect fertility or reproductive performance in rats, nor was it teratogenic in rats (up to 400 mg/kg/day) or rabbits (up to 100 mg/kg/day). However, at doses ≥ 100 mg/kg/day in male rats a decrease in the sperm straight line velocity was observed, while in female pregnant rats a decrease in number of viable foetuses and increase in early resorptions and post-implantation losses were observed, likely due to maternal toxicity. In a pre- and postnatal developmental toxicity study in rats, decreased pup survival due to poor maternal care and reduced body weight gain associated with a delay in developmental milestones were observed at doses ≥ 150 mg/kg/day. However, the subsequent fertility and mating performance of these offspring, and their ability to maintain pregnancy and to deliver live offspring, were unaffected by maribavir.	Maribavir did not have an effect on fertility and is not considered to be teratogenic. *Breast-feeding* It is unknown whether maribavir or its metabolites are excreted in human milk.
Genotoxicity:	
Maribavir was not mutagenic in the bacterial mutation assay but demonstrated mutagenic potential in the absence of metabolic activation in the mouse lymphoma assay. However, in rat bone marrow micronucleus assay, maribavir was not clastogenic up to a very high oral dose of 1200 mg/kg that elicited toxicity. Based on the totality of evidence from the studies conducted, maribavir is not considered to be genotoxic.	The weight of evidence from in-vitro and in-vivo genotoxicity studies indicate that maribavir does not exhibit genotoxic potential.
Carcinogenicity:	
Maribavir was not carcinogenic in the 2-year study in rats up to 100 mg/kg/day. No neoplastic lesions were observed up to doses of 300 mg/kg/day in the 13-week oral toxicity study in CD-1 mice. However, in a 2-year study in CD-1 mice, an equivocal increase in the incidence of hemangioma, hemangiosarcoma, and combined hemangioma/hemangiosarcoma across multiple tissues was noted in males given 150 mg/kg/day (high dose). These findings	For the treatment of CMV infection, maribavir will be administered to transplant patients twice a day for 8 weeks. Hence the increased incidence of hemangioma/hemangiosarcoma in male mice following daily administration for 104 weeks is of uncertain relevance in terms of its translation to human risk given the difference in frequency of administration and the lack of an effect in female mice or in rats after 104 weeks of administration, lack of any proliferative effects in male and female mice after 13 weeks of administration, and the negative genotoxicity

Key Safety Findings	Relevance to human usage
were not observed at doses ≤ 75 mg/kg/day.	package.
Safety pharmacology:	
In a series of safety pharmacology studies maribavir had no major effects on the central nervous system, cardiovascular, respiratory, or autonomic functions. There was no effect on human ether-a-go-go related gene (hERG) currents up to the highest maribavir concentration of 1254 µg/mL. The cardiovascular, respiratory and autonomic function were evaluated in the anesthetized dogs. At a bolus dose of maribavir 43 mg/kg there were increases in heart rate, with no significant effect on mean arterial pressure. A transient increase in respiratory rate and volume was observed that returned to pre-drug levels. There was no effect on autonomic function. ECGs were not evaluated in this study. A CV-telemetry study in animal models to assess the effects of maribavir on QTc intervals was not conducted. However, in a definitive TQT study in healthy human subjects, maribavir did not have clinically significant effects on repolarization (QTc interval) or other electrocardiographic parameters at 100 mg and 1200 mg doses. The positive control moxifloxacin demonstrated the expected effects and assay sensitivity.	No evidence of potential human risk to central nervous system (CNS), cardiovascular (CV), respiratory or autonomic functions.
Other toxicity-related information or data:	
Immunogenicity	
Maribavir did not demonstrate any immunological liability in rats at doses up to 100 mg/kg/day.	Maribavir is considered not to have an any immunotoxic potential.
Phototoxicity	
In-vitro maribavir was not phototoxic at concentrations up to 100 µg/mL in BALB/c 3T3 mouse fibroblasts.	The potential for phototoxicity is considered unlikely.
Drug-Drug Interaction	
In-vitro maribavir is a weak time-dependent inhibitor for cytochrome P450 (CYP)3A4 and	Maribavir can be dosed with CYP3A inhibitors without dose adjustment, however, to ensure

Key Safety Findings	Relevance to human usage
weak inducer of CYP3A4. PBPK modeling predicted a less than 2-fold increase in systemic exposure to maribavir following concomitant administration of CYP3A4 inhibitors such as ketoconazole, ritonavir, erythromycin, and diltiazem. However, CYP3A inducers significantly reduce maribavir exposure; therefore, to ensure antiviral efficacy (using the BID trough concentration at 12 hours as the marker), maribavir dose increase is necessary when concomitant administration with CYP3A inducers is needed.	antiviral efficacy dose increase is necessary when concomitant administration with CYP3A inducers is needed.
Mechanism for Drug Interactions	
Maribavir is an in-vitro substrate of CYP3A4 and to a minor extent by CYP1A2 and uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A3, UGT2B7, possibly UGT1A9, P-glycoprotein (P-gp), organic cation transporter (OCT) 1, and breast cancer resistant protein (BCRP). In-vitro maribavir is a weak time-dependent inhibitor of CYP3A4 (nifedipine but not midazolam or testosterone), and weak inhibitor of CYP1A2, CYP2C9 and CYP2C19, P-gp, BCRP, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OCT1, organic anion transporter (OAT) 3, multidrug and toxin extrusion transporter (MATE)1, and bile salt export pump. Maribavir is also a moderate inhibitor of BCRP. In vitro, Maribavir is a weak inducer of CYP3A4 and CYP1A2, but not CYP2B6.	The potential for drug-drug interactions is considered to be low and dose adjustment of maribavir is only needed when maribavir is concomitant administered with a strong or moderate CYP3A4 inducer. With the exception of selected immunosuppressants, digoxin and rosuvastatin, concomitant administration with maribavir does not impact the use or outcomes of a wide range of other drugs commonly used in the target patient population (refer to Section SVII).

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Duration of exposure

Cumulative duration of exposure for Treatment of CMV indication (person time)		
Duration of exposure[1] (Exposure to maribavir)	Patients	Person time (day)[2]
Median (min, max) days	57 (2, 64)	-
Distribution of days of exposure (days)		
1 to 14	10	95
15 to 28	11	285
29 to 42	8	285
43 to 56	83	4,463
>56	144	8,331
Total person time	**256**	**13,389**

[1] Exposure duration: Number of days between the date of the first dose and the date of last dose of maribavir.

[2] Person time (day) is defined as the total number of days of exposure for all subjects who received maribavir 400mg BID either as the study assigned treatment or as rescue treatment in 303 study.

Table SIII.2: Estimated Cumulative Subject Exposure to Maribavir from Completed Clinical Studies by Age and Gender[1]

	Number of Subjects		
Age Range (years)	**Male**	**Female**	**Total**
<18	0	0	0
18 – 44	348	221	569
45 – 64	514	299	813
>64	115	58	173
Unknown	0	0	0
Total	**977**	**578**	**1,555**

[1]Data from all maribavir completed studies.

Table SIII.3: Dose

	Maribavir dose (in mg)								
Study type	**50**	**100**	**200**	**400**	**600**	**800**	**900**	**1,200**	**1,600**
Phase 1									
Single-Dose Studies (Healthy, Renally Impaired, Hepatically Impaired)[1]	-	66	40	138	-	-	-	51	-
Single-Dose, Dose-Escalation Studies (Healthy & HIV)[2]	10	22	10	23	-	22	-	-	22
Multiple-Dose Studies (Healthy & Renal Transplant Recipients)[3]	-	-	17	70	-	-	-	-	-
Multiple-Dose Studies (HIV)[4]	-	11	12	10	7	4	12	14	-
Phase 1 total subjects[5]	**380**								
Phase 2 & 3 (Transplant Recipients)									

	Maribavir dose (in mg)								
Study type	**50**	**100**	**200**	**400**	**600**	**800**	**900**	**1,200**	**1,600**
1263-200	-	28	-	54	-	-	-	-	-
1263-202	-	-	-	40	-	40	-	40	-
1263-203	-	-	-	40	-	40	-	39	-
1263-300	-	451	-	-	-	-	-	-	-
1263-301	-	147	-	-	-	-	-	-	-
SHP620-303	-	-	-	256	-	-	-	-	-
Phase 2 & 3 Total Subjects[5]	**1,175**								
Total Subjects Exposed to Maribavir[5]	**1,555**								

Note: Table includes subjects from completed studies: 1263-100, 1263-101, 1263-102, 1263-103, 1263-104, 1263-105, 1263-106, 1263-107, 1263-108, 1263-109, 1263-110, 1263-115, 1263-200, 1263-300, 1263-301, 1263-202, 1263-203, SHP620-303, CMAB-1001, CMAB-1002, CMAA-1003, CMAA-1004, TAK-620-1019. Data from all completed maribavir studies.

[1] Studies 1263-101, 1263-102, 1263-103, 1263-104, 1263-106, 1263-108, 1263-109, TAK-620-1019.

[2] Studies CMAB-1001, CMAB-1002; Includes study designs in which a given subject may have received more than one dose regimen; subjects are counted once in each group in which they received a dose.

[3] Studies 1263-100, 1263-105, 1263-107, 1263-110, 1263-115.

[4] Studies CMAA-1003, CMAA-1004.

[5] Number of subjects exposed to any one or more dose regimens of maribavir.

Table SIII.4: Estimated Cumulative Subject Exposure to Maribavir from Completed Clinical Studies by Ethnic Group[1]

Ethnic Group	Number of Subjects
American Indian or Alaskan Native	2
Asian	35
Black or African American	162
Native Hawaiian or Other Pacific Islander	7
White	1,313
Other	34
Unknown	2
Total	**1,555**

[1]Data from all maribavir completed studies.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Table SIV.1:Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
Pregnant or Lactating Women.	There is no clinical experience with maribavir in pregnant or nursing women. Therefore, the possibility of foetal harm during pregnancy is not known. It is unknown whether maribavir is excreted in human milk and has effect on breast-fed infant.	No	Maribavir is not recommended during pregnancy and in women of childbearing potential not using contraception. Moreover, breast feeding should be discontinued during treatment with maribavir. Thus, there is no anticipated utilisaton in these populations
Use in patients with severe hepatic impairment.	Subjects with Aspartate Aminotransferase (AST) >5x Upper limit of normal (ULN) or Alanine aminotransferase (ALT) > 5x ULN or total bilirubin >/= 3x ULN were excluded from clinical studies. There is no experience with the use of maribavir in subjects with severe hepatic impairment.	No	In study 1263-103, patients with moderate hepatic impairment showed substantially slower elimination and higher plasma concentrations of maribavir than healthy patients given the same dose. However, this increased exposure to maribavir is not considered clinically significant. It is expected that severe hepatic impairment will not lead to a clinically relevant increase of maribavir exposure.
Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis.	There is no experience with the use of maribavir in subjects with ESRD including peritoneal dialysis or haemodialysis. Subjects in the clinical studies were post-transplant and not on dialysis. Subjects with renal dysfunction that had	Yes	Not applicable.

Table SIV.1:Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
	estimated glomerular filtration rate (eGFR) >30 mL/min/1.73m^2 were included.		
Use in patients with tissue invasive CMV disease with CNS involvement (including retinitis).	Based on pre-clinical data, maribavir is not expected to cross the blood brain barrier in sufficient concentrations to treat CMV in the CNS.	No	Maribavir CNS penetration is unlikely and based upon the limited PK data in nonclinical studies, maribavir levels in the CNS are expected to be low relative to plasma levels. Maribavir is not expected to be effective in treating CMV CNS infections (e.g., meningo encephalitis)
Use in patients with known positive results for human immunodeficiency virus (HIV).	Positive results for HIV is considered a clinically significant medical condition that could interfere with the subject's ability to comply with the requirements of the study or compromise the safety or well-being of the subject.	No	Phase 1 studies were conducted in 3 single- and multiple-dose studies in HIV-positive subjects and subjects with AIDS. The most common treatment-emergent adverse event (TEAE) was taste disturbance (dysgeusia) similar to what was reported in the program. There is no expectation the safety to differ in HIV positive subjects compared to the general population of transplant recipients.

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	The average childbearing age, as defined by World Health Organization, is from 18-44 years. Refer to the Table SIII.2 for details on women of childbearing age.
Patients with relevant co-morbidities:	
Patients with hepatic impairment	Subjects with severe hepatic impairment were not included in the clinical development program. A Phase I open label study was conducted in subjects with moderate hepatic impairment (10 Subjects) versus normal hepatic function (10 Subjects) with 200 mg dose. Modest increases in maribavir total and unbound exposure in subjects with moderate hepatic impairment were not considered clinically significant.
Patients with renal impairment	A Phase I single-dose study with 400 mg maribavir dose was conducted in renally impaired (10 subjects with mild/moderate, 9 subjects with severe renal impairment) versus normal renal function (12 subjects) subjects. Mean PK parameter estimates based on total or unbound plasma drug concentrations for subjects with normal renal function (creatinine clearance >80 mL/min), mild/moderate renal impairment (30-80 mL/min), and severe renal impairment (<30 mL/min) were similar.
Patients with cardiovascular impairment	Subjects who required mechanical ventilation or vasopressors for hemodynamic support (at the time of enrollment) were not included in clinical development program.
Immunocompromised patients	The study population in the program were immunocompromised patients. There is no data in transplant patients with co-infection with HIV or HCV. Patients with HIV or HCV co-infection were excluded in Phase 3 studies.

Type of special population	Exposure
Patients with a disease severity different from inclusion criteria in clinical trials	Study-620-203 included subjects that did not have tissue invasive CMV disease or CMV syndrome.
Population with relevant different ethnic origin	Refer to the Table SIII.4 for exposure detail. Ethnicity (Hispanic/Latino vs non-Hispanic/Latino) did not have a clinically significant effect on the PK of maribavir.
Subpopulations carrying relevant genetic polymorphisms	Maribavir is primarily metabolized by CYP3A4 isozyme. No effect of genetic polymorphism of CYP3A4 on maribavir PK is expected.
Other	
Geriatric patients	Refer to the Table SIII.2 for details on geriatric patient's exposure. Based on the population PK analysis, there was no clinically relevant impact on maribavir PK exposure, the steady-state Area Under the Curve (AUC) and C_{max} in patients aged >65 years and patients aged between 18 and 65 years.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Maribavir does not have potential for misuse for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- Taste disturbance (ageusia, dysgeusia, hypogeusia and taste disorder),
- Headache,
- Abdominal pain upper,
- Decreased appetite.

Taste disturbance (ageusia, dysgeusia, hypogeusia and taste disorder) is very commonly reported as a non-serious adverse reaction. These adverse events rarely led to drug discontinuation (0.9%). For most patients, taste disturbance resolved while patients remained on therapy (37%) or resolved at a median of 7 days (Kaplan-Meier estimate, 95% CI: 4, 8) off treatment.

Headache, abdominal pain upper and decreased appetite are 'commonly' reported as non-serious adverse reaction. All these events are listed in Section 4.8 of the Summary of Product Characteristic (SmPC) but are not associated with a relevant risk.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Taste disturbance
- Headache
- Diarrhoea, nausea, vomiting
- Abdominal pain upper
- Fatigue
- Decreased appetite
- Weight decreased

The most 'common' and 'very common' reported adverse reactions were taste disturbance; headache; diarrhoea, nausea, vomiting; abdominal pain upper, fatigue, decreased appetite, weight decreased, and immunosuppressant drug concentration increased.

All these events are listed in Section 4.8 of the SmPC but are not associated with a relevant risk except for immunosuppressant drug concentration increased which is described below in SVII.1.2.

Known risks that do not impact the risk-benefit profile

If co-administration of LIVTENCITY with other strong or moderate CYP3A inducers (e.g., carbamazepine, efavirenz, phenobarbital and phenytoin) cannot be avoided, the LIVTENCITY dose should be increased to 1200 mg twice daily with the exception of selected immunosuppressants,

rosuvastatin, and digoxin, concomitant administration with maribavir does not impact the use or outcomes of a wide range of other drugs commonly administered in the target patient population.

Other reasons for considering the risks not important:

Drug-Drug Interaction with statins: In-vitro data showed that maribavir is an inhibitor of BCRP (IC50 = 7.05µM). Based on physiologically based pharmacokinetic (PBPK) modeling results, concomitant administration of 400 mg BID maribavir with rosuvastatin, a sensitive BCRP substrate, is expected to increase rosuvastatin AUC by 2.15- to 2.94-fold, and C_{max} by 3.40- to 4.97-fold. However, in Phase 2 and Phase 3 studies, there was no increased risk of musculoskeletal disorders when maribavir was concomitantly administered with rosuvastatin or other commonly used statins in transplant patients with CMV infections (Module.2.7.2). Therefore, there is a possibility that PBPK may overpredict the in vivo effect of maribavir on rosuvastatin PK. This is discussed in SmPC Section 4.4; Section 4.5; and Package leaflet.

Drug-Drug Interaction with digoxin: Maribavir is an in vitro inhibitor of P-glycoprotein (P-gp) transporter. In a clinical study, co-administration of LIVTENCITY increased plasma concentrations of digoxin: increased AUC by 21% and Cmax by 25%. Given the narrow therapeutic window of digoxin, caution should be exercised when LIVTENCITY and digoxin are co administered. Serum digoxin concentrations should be monitored, and dose of digoxin may need to be reduced, as needed. (see Section 4.4 and 4.5 of the SmPC)

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk	Risk-benefit impact
Not applicable.	

Important Potential Risk	Risk-benefit impact
Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	During the clinical development program, it was observed that concomitant administration of maribavir with tacrolimus resulted in increased tacrolimus C_{max} and AUC by 33% and 54% respectively. Approximately 10% of subjects in the pivotal 303 Study showed this adverse event of special interest (AESI) and most AESI were mild to moderate in severity. Thus, there is a potential to increase the drug concentrations of other immunosuppressants with a narrow therapeutic window (including cyclosporine, sirolimus and everolimus). This DDI could result in toxicities from elevated immunosuppressant levels (for example, infections, worsening of renal function which may lead to acute renal failure in severe cases). The risk of DDI can be mitigated by frequently monitoring of immunosuppressant drug levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjusting the dose as required. The post-authorisation safety profile will be evaluated through the routine pharmacovigilance activities.

Missing Information	Risk-benefit impact
Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis	There is no experience of use of maribavir in patients with ESRD including peritoneal dialysis or haemodialysis. Due to limited experience, use of maribavir in this subpopulation is assessed as a missing information.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	
Potential mechanisms:	Concomitant administration of maribavir with tacrolimus increases exposure to tacrolimus, and this is most likely due to inhibition of CYP3A4 activity, P-glycoprotein or both.
Evidence source(s) and strength of evidence:	LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A and/or P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporine, sirolimus and everolimus). In clinical trials, immunosuppressant drug level increase has been commonly reported while very few led to a serious adverse drug reaction.
Characterisation of the risk:	Maribavir is metabolized primarily in the liver and is a substrate of CYP 3A4 and the transport protein P- gp. In-vitro, maribavir is an inhibitor of P- gp (IC50 = 33.7 µM). A Phase 1 clinical study (Study 1263-105) conducted to evaluate the potential of drug-drug interactions demonstrated the following: Concomitant administration of maribavir (400 mg BID) with tacrolimus, a substrate of CYP 3A4 and P- gp, resulted in increased tacrolimus C_{max} and AUC by 33% and 54%, respectively. Administration of maribavir to healthy subjects indicated that maribavir is not a significant inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 and is a weak inhibitor of CYP2C19 and P-gp.

Important Potential Risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	
	SHP620-202 In clinical study SHP620-202, 12/120 (10%) of all subjects who received maribavir experienced the adverse event of immunosuppressant drug level increased (ISDLI). The number (%) of subjects reporting this adverse event (AE) were 4 (10%), 2 (5%), and 6 (15%) in the maribavir 400 mg BID, 800 mg BID, and 1200mg BID groups, respectively. Eleven of these 12 subjects had events that were considered by the investigator to be related to maribavir therapy. The majority of events were mild to moderate in intensity; however, 3 subjects (1 subject in 800mg BID group and 2 subjects in 1200 mg BID group) had events severe in intensity. One treatment-emergent serious adverse event (SAE) of acute kidney injury secondary to increased tacrolimus levels was reported in the subject who was in 1200 mg BID group and the subject discontinued maribavir. SHP620-203 In clinical study SHP620-203, 10/119 (8.4%) of all subjects treated with maribavir experienced ISDLI. The incidence of this event was 2/40 (5%), 2/40 (5%) and 6/39 (15.4 %) in the 400 mg BID, 800 mg BID, and 1200 mg BID groups, respectively. This was not reported in the valganciclovir cohort. This was reported as related with 2 dose cohorts (800 mg and 1200 mg) of maribavir in 4/119 (3.4%). Four subjects had events that were considered by the investigator to be related to maribavir and this included the 2 subjects in the 1200 mg BID who had severe symptoms. One event led to drug interruption in 800 mg BID dose. Two subjects in the 1200 mg BID group experienced severe symptoms (cachexia and toxic encephalopathy in one subject and ISDLI in the other subject). One treatment-emergent SAE of increasing tacrolimus levels was reported in the subject who was in 1200 mg BID group and the subject discontinued maribavir. SHP620-303 The TEAE of ISDLI was reported in a higher proportion of subjects in the maribavir group (21/234, 9.0%) compared to the investigator-assigned anti-CMV treatment (IAT) group (1/116, 0.9%). In

Important Potential Risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	
	6% (14 subjects), this TEAE was assessed as related to treatment in maribavir group and none in IAT group. It was reported as a treatment-emergent serious adverse event (SAE) for 1 (0.4%) maribavir-treated subject. Amongst the 21 maribavir-treated subjects who had increased ISDLI reported as a TEAE, 19 subjects had tacrolimus concentration increased and 2 had sirolimus concentration increased. This TEAE was reported as severe for 2 subjects (tacrolimus), moderate for 6 subjects (tacrolimus), and mild for 13 subjects (11 for tacrolimus and 2 for sirolimus). Mean values of immunosuppressant drug levels varied across the study time points and did not show any consistent trends for increased immunosuppressant drug levels with maribavir treatment.
Risk factors and risk groups:	It is likely that AE of ISDLI is dose-dependent, and patient on the highest doses of maribavir are at highest risk for drug interaction between maribavir and ISD. As this is a known interaction and has been formally studied, adjustment of the doses of ISD can be made. However, there is a need for more extensive monitoring of ISD concentration levels and potential for more frequent dose adjustments.
Preventability:	Frequently monitor immunosuppressant drug (including tacrolimus, cyclosporine, sirolimus and everolimus) levels throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and adjust the dose, as needed.
Impact on the risk-benefit balance of the product:	During the clinical development program, it was observed that concomitant administration of maribavir with CYP3A and/or P-gp substrate tacrolimus resulted in increased tacrolimus C_{max} and AUC by 33% and 54% respectively, thus there is a potential to increase the drug concentrations of other immunosuppressants with a narrow therapeutic window (including tacrolimus, cyclosporine, sirolimus and everolimus). This DDI could result in toxicities (for example, infections, worsening of renal function which may lead to acute renal failure in severe cases). The risk of DDI could be mitigated with the provision of specific guidance concerning this risk in label.

Important Potential Risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	
Public health impact:	Low.

SVII.3.2. Presentation of the missing information

Missing information: Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis	
Evidence source:	Subjects with renal dysfunction that had eGFR > 30 mL/min/1.73m^2 were included in Phase 2/3 studies. Subjects with ESRD including subjects on peritoneal dialysis or haemodialysis were excluded from the clinical development program; therefore, there is no clinical trial experience in this subpopulation.
Population in need of further characterisation:	Patients with ESRD including patients on peritoneal dialysis or haemodialysis.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level
Missing information	• Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Yes, a specific adverse reaction follow-up questionnaire for important potential risk of increased risk of serious adverse reactions due to an increase in immunosuppressant drug level will be sent.

Other forms of routine pharmacovigilance activities for safety concerns:

None.

III.2. Additional pharmacovigilance activities

Study SHP620-302	
Study short name and title	A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients
Rationale and study objectives	Primary Objective The primary objective of the study is to compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in HSCT recipients. The secondary objectives are: • To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance after completion of 8 weeks of treatment for asymptomatic CMV infection in HSCT recipients. • To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved after completion of 8 weeks of treatment, through Study Weeks 12 (4 weeks of post-treatment period), 16 (8 weeks of post-treatment/follow-up phase), and 20 (12 weeks post-treatment). • To assess the maintenance of CMV viremia clearance, achieved at the end of Study Week 8, through Weeks 12 (4 weeks of post-treatment period), and 20 (12 weeks post-treatment). • To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms during the first 8 weeks of the study, during the 12 weeks of the follow-up study phase, and at any time during the study. • To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment arms when subjects are on treatment and off treatment. • To evaluate the incidence of treatment-emergent grade 3 or 4 neutropenia (defined as ANC<1000/mm^3 or ANC<500 /mm^3) while on treatment.

Study SHP620-302	
	• To assess the safety and tolerability of maribavir compared to valganciclovir. • To characterize the PK of maribavir.
Study design	Multicenter, randomized, double-blind, double-dummy, active-controlled study
Study population	Approximately 550 subjects, ≥16 years of age, who are HSCT recipients with asymptomatic CMV infections will be enrolled. Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.
Milestone(s)	Final study report: February 2023

Study Number TBD	
Study short name and title	Retrospective chart review study on safety outcomes associated with use of maribavir in patients with post-transplant refractory or resistant cytomegalovirus (CMV) infection and having end-stage renal disease (ESRD) including patients on peritoneal dialysis or haemodialysis.
Rationale and study objectives	Safety of maribavir in the treatment of patients with CMV disease post-transplant has been previously demonstrated, but the effect of ESRD on maribavir safety remains unknown. Primary objective: Evaluate the known and potential safety risks for patients treated with maribavir who also have end-stage renal disease including patients on peritoneal dialysis or haemodialysis.
Study design	Retrospective chart review
Study population	European patients who have undergone solid organ (SOT) or hematopoietic (HSCT) transplant and who have been diagnosed with refractory or resistant CMV during the post-transplant period and have comorbid ESRD.
Milestone(s)	Protocol submission: Q2 2023

III.3. Summary Table of additional Pharmacovigilance Activities

Table Part III.1: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
the marketing authorisation				
Not applicable.	Not applicable.	Not applicable.	Not applicable.	Not applicable.
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.	Not applicable.	Not applicable.	Not applicable.	Not applicable.
Category 3 - Required additional pharmacovigilance activities				
SHP620-302: A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients. Ongoing	Primary Objective The primary objective of the study is to compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in HSCT recipients. A list of secondary objectives can be found in Annex 2	Important potential risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level.	Final study report	February 2023.
Study number TBD Retrospective chart review study on safety outcomes associated with use of maribavir in patients with post-transplant refractory or resistant cytomegalovirus	Evaluate the known and potential safety risks for patients treated with maribavir who also have end-stage renal disease including patients on peritoneal dialysis or	Missing Information: Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis	Protocol submission	Q2 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
(CMV) infection and having end-stage renal disease (ESRD) including patients on peritoneal dialysis or haemodialysis. Planned	haemodialysis.			

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies which are conditions of the marketing authorisation				
Not applicable.	Not applicable.	Not applicable.	Not applicable.	Not applicable.
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.	Not applicable.	Not applicable.	Not applicable.	Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	**Routine risk communication:** SmPC Section 4.4; Section 4.5; and Section 4.8. PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The prescribers are informed of the potential for increased immunosuppressant drug level while patients are on maribavir therapy. The prescribers are advised to frequently monitor immunosuppressant drug level throughout LIVTENCITY treatment, especially following initiation and after discontinuation of LIVTENCITY and adjust the dose, as required. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine.
Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis	**Routine risk communication:** SmPC Section 4.2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1. Routine Risk Minimisation Measures are sufficient to manage the safety concerns of the medicinal product.

Objectives:

Not applicable.

Rationale for the additional risk minimisation activity:

Not applicable.

Target audience and planned distribution path:

Not applicable.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Not applicable.

Removal of additional risk minimisation activities:

Not applicable.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	**Routine risk minimisation measures:** SmPC Section 4.4, Section 4.5, Section 4.8 and PL Section 2. The prescribers are informed of the potential for increased immunosuppressant drug level while patients are on maribavir therapy. The prescribers are advised to frequently monitor level of these immunosuppressant drugs (sirolimus, tacrolimus, everolimus, and cyclosporine) throughout treatment, especially following initiation and after discontinuation of LIVTENCITY and adjust the dose, as required. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Immunosuppressant drug level increased (IDLI) Questionnaire **Additional pharmacovigilance activities:** Clinical study SHP620-302.
Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis	**Routine risk minimisation measures:** SmPC Section 4.2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Planned Retrospective chart review study (Study number TBD).

Part VI: Summary of the risk management plan

Summary of risk management plan for LIVTENCITY (Maribavir)

This is a summary of the risk management plan (RMP) for LIVTENCITY. The RMP details important risks of LIVTENCITY, how these risks can be minimised, and how more information will be obtained about LIVTENCITY's risks and uncertainties (missing information).

LIVTENCITY's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LIVTENCITY should be used.

This summary of the RMP for LIVTENCITY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of LIVTENCITY's RMP.

I. The medicine and what it is used for

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that is refractory (with or without resistance) to one or more prior therapies, including ganciclovir, valganciclovir, cidofovir or foscarnet in adult patients who have undergone a haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT).

Further information about the evaluation of LIVTENCITY's benefits can be found in LIVTENCITY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: *LINK TO THE EPAR SUMMARY LANDING PAGE*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of LIVTENCITY, together with measures to minimise such risks and the proposed studies for learning more about LIVTENCITY's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of LIVTENCITY is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of LIVTENCITY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LIVTENCITY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been

established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level
Missing information	• Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis

II.B Summary of important risks

Important potential risk: Increased risk of serious adverse reactions due to an increase in immunosuppressant drug level	
Evidence for linking the risk to the medicine	LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A and/or P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporine, sirolimus and everolimus). In clinical trials, immunosuppressant drug level increase has been commonly reported while very few led to a serious adverse drug reaction.
Risk factors and risk groups	It is likely that this phenomenon is dose dependent, and patients on the highest doses of maribavir are at highest risk for drug interactions when maribavir is administered concomitantly with the immunosuppressant drug.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4, Section 4.5, Section 4.8 and PL Section 2. The prescribers are informed of the potential for increased immunosuppressant drug levels (tacrolimus, sirolimus, everolimus, cyclosporine) while on maribavir therapy. The prescribers are advised to frequently monitor these immunosuppressant drug levels throughout LIVTENCITY treatment, especially following initiation and after discontinuation of LIVTENCITY and adjust the immunosuppressant dose, as required. **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Clinical study SHP620-302.

Missing information: Use in patients with end stage renal disease (ESRD) including peritoneal dialysis or haemodialysis	
Risk minimisation measures	**Routine risk minimisation measures** SmPC Section 4.2. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Planned Retrospective chart review study (Study number TBD).

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

Not applicable.

II.C.2. Other studies in post-authorisation development plan

SHP620-302: A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients.

Purpose of the study: The primary objective of the study is to compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in HSCT recipients. A list of secondary objectives can be found in Annex 2.

Study number TBD (planned): Retrospective chart review study on safety outcomes associated with use of maribavir in patients with post-transplant refractory or resistant cytomegalovirus (CMV) infection and having end-stage renal disease (ESRD) including patients on peritoneal dialysis or haemodialysis.

Purpose of the study: Safety of maribavir in the treatment of patients with CMV disease post-transplant has been previously demonstrated, but the effect of ESRD on maribavir safety remains unknown. Primary objective: Evaluate the known and potential safety risks for patients treated with maribavir who also have end-stage renal disease including patients on peritoneal dialysis or haemodialysis.

Part VII: Annexes

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Annex 4: Specific adverse drug reaction follow-up forms

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GLOBAL FORM

Form Number:	**FORM-xxxxx (received from LEADS)**	**Page:**	1 of 8
Version Number:	**1.0**		
Parent Document:	TOOL-0003834		
Title:	**Global Form, Immunosuppressant drug level increased (IDLI) Questionnaire**		

Was immunosuppressant drug level increased? ☐ **Yes** ☐ **No.**
If yes, please answer following questions.

Case ID:	**Send completed questionnaire by email to Takeda at:** _____

1. CASE TYPE

☐ Spontaneous ☐ Pregnancy ☐ Lactation ☐ Regulatory Authority ☐ Observational Study
☐ Clinical Study, if checked: Protocol No.: EudraCT No.: Study Title:

2. PATIENT INFORMATION

Date of Birth (dd/mm/yyyy)	**Age**	**Gender**	**Ethnicity/Race**	**Weight**	**Height**
		☐ Male ☐ Female		☐kg ☐ lb	☐cm ☐in

3. PRODUCT INFORMATION

Product Name	**Unit Dose**	**Form**	**Route**	**Frequency**	**Drug Product Lot#/ Ser#**	**Dates (dd/mm/yyyy)**	**Indication**	**Action Taken with Drug**
Maribavir						Start: Stop:		
Immunosuppressant drug Tacrolimus						Start: Stop:		
Immunosuppressant drug Cyclosporine						Start: Stop:		
Immunosuppress						Start:		

Case ID:						**Send completed questionnaire by email to Takeda at:** _____		
ant drug Sirolimus						Stop:		
Immunosuppressant drug Everolimus						Start: Stop:		
Additional Space								

4. IMMUNOSUPPRESSANT DRUG INFORMATION: Complete sections 4a, 4b and 4c

4a. Immunosuppressant drug level IMMEDIATELY BEFORE maribavir initiation	
Date and time:	
Immunosuppressant drug:	☐Tacrolimus ☐Cyclosporine ☐Sirolimus ☐Everolimus
Drug level (include value & unit):	
Target therapeutic range:	
4b. Immunosuppressant drug level DURING maribavir treatment	
Date and time:	
Immunosuppressant drug:	☐Tacrolimus ☐Cyclosporine ☐Sirolimus ☐Everolimus
Drug level (include value & unit):	
Target therapeutic range (if changed):	
Was the immunosuppressant dose adjusted?	☐No ***If checked, state reason(s):*** ☐Yes ***If checked, continue to next question***
Was the immunosuppressant dose adjusted due to an AE?	☐No ***If checked, state reason(s):***

Case ID:	**Send completed questionnaire by email to Takeda at:** _____

	☐Yes ***If checked, list AE(s) in SECTION 5***
Date and time:	
Immunosuppressant drug:	☐Tacrolimus ☐Cyclosporine ☐Sirolimus ☐Everolimus
Drug level (include value & unit):	
Target therapeutic range (if changed):	
Was the immunosuppressant dose adjusted?	☐No ***If checked, state reasons:*** ☐Yes ***If checked, continue to next question***
Was the immunosuppressant dose adjusted due to an AE?	☐No ***If checked, state reason(s):*** ☐Yes ***If checked, list AE(s) in SECTION 5***
Date and time:	
Immunosuppressant drug:	☐Tacrolimus ☐Cyclosporine ☐Sirolimus ☐Everolimus
Drug level (include value & unit):	
Target therapeutic range (if changed):	
Was the immunosuppressant dose adjusted?	☐No ***If checked, state reasons:*** ☐Yes ***If checked, continue to next question***
Was the immunosuppressant dose adjusted due to an AE?	☐No ***If checked, state reason(s):*** ☐Yes ***If checked, list AE(s) in SECTION 5***

Case ID:	**Send completed questionnaire by email to Takeda at:** _____

Attach additional pages as needed for additional Immunosuppressant drug level DURING maribavir treatment

4c. Immunosuppressant drug level AFTER maribavir discontinuation (provide number of
days within two weeks after stopping

Date and time:	
Immunosuppressant drug:	☐Tacrolimus ☐Cyclosporine ☐Sirolimus ☐Everolimus
Drug level (include value & unit):	
Target therapeutic range (if changed):	
Was the immunosuppressant dose adjusted?	☐No ***If checked, state reasons:*** ☐Yes ***If checked, continue to next question***
Was the immunosuppressant dose adjusted due to an AE?	☐No ***If checked, state reasons:*** ☐Yes ***If checked, list AE(s) in SECTION 5***

Additional Space

5. ADVERSE EVENT INFORMATION

Adverse Event(	**Dates (dd/mm/yyyy)**	**Serious Crit**	**Severity of**	**Event Outc**	**Reporter Caus**	**De-challenge**	**Re-challenge**

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s) or Diagnosis or abuse, misuse, overdose, medication error		**eria**	**the event**	**ome**	**ality**		
	Start: **Stop:**						
	Start: **Stop:**						
	Start: **Stop:**						
	Start: **Stop:**						
	Start: **Stop:**						
	Start: **Stop:**						
	Start: **Stop:**						

Case ID:	**Send completed questionnaire by email to Takeda at:** _____

	Start: **Stop:**						

Additional Space

6. IN-PATIENT HOSPITALIZATION / DEATH (complete only if patient was admitted to hospital, or died)

A. Patient was Hospitalized:
- ☐ Due to the Adverse Event
- ☐ Before the event, but Hospitalization was Prolonged due to the Event
- ☐ Before the event, but Hospitalization was not Prolonged Due to the Event
- ☐ Not Due to the Event

Reason not Due to the Event:
Admission Date (dd/mm/yyyy): Discharge Date (dd/mm/yyyy):
Duration of Hospitalization (days):
☐ Hospital Report is on local file and available upon request Unavailable

B. Complete this Section if Patient Died:
Date of Death (dd/mm/yyyy): Cause(s) of Death:
Autopsy Performed? Autopsy Date (dd/mm/yyyy):
☐ Autopsy Report on local file and available upon request Unavailable

7. CONCOMITANT AND TREATMENT MEDICATIONS (relevant to the AE) – Include treatment meds below and select Treatment medication or Concomitant medication

Drug Name	**Treatment medication**	**Concomitant medication**	**Dose**	**Form**	**Route**	**Frequency**	**Dates** (dd/mm/yyyy)	**Indication**	**Ongoing?**
							Start: Stop:		☐ Yes ☐ No

Case ID:	**Send completed questionnaire by email to Takeda at:** _____

							Start: Stop:		☐ Yes ☐ No
							Start: Stop:		☐ Yes ☐ No
							Start: Stop:		☐ Yes ☐ No
							Start: Stop:		☐ Yes ☐ No

8. EVENT DESCRIPTION

Please provide a detailed case narrative in chronological order. For follow-up information, indicate the date (dd/mm/yyyy) when new information was received:

9. INVESTIGATION TRACKING INFORMATION

Additional Information:	☐Has been requested ☐Will be requested from reporter
No Additional Information:	☐Has been requested, or ☐Will not be requested from reporter for the following reasons: ☐Information that was provided was sufficient ☐Reporter refused to provide further information ☐Other reason, please specify

10. ADDITIONAL INFORMATION

Case ID:	**Send completed questionnaire by email to Takeda at:** _____

11. Completed By	Print Name:	Today's Date (dd/mm/yyyy):
	Signature:	
	Reporter type: ☐ Physician ☐ Nurse ☐ Pharmacist ☐ Other Health Care Professional (HCP) ☐ Consumer ☐ Non-HCP caregiver (pls specify:_____) Unknown ☐	
	Address:	
	Contact Number:	Email

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.