Summary Report of Benefit-Risk Assessment

LIVTENCITY FILM-COATED TABLET 200MG

NEW DRUG APPLICATION

Active Ingredient(s)	Maribavir
Product Registrant	TAKEDA PHARMACEUTICALS (ASIA PACIFIC) PTE. LTD.
Product Registration Number	SIN17208P
Application Route	Abridged evaluation
Date of Approval	18 March 2025

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A INTRODUCTION

Livtencity is indicated for the treatment of adults with post-transplant cytomegalovirus (CMV) infection/disease, who are refractory (with or without genotypic resistance) or intolerant to one or more prior therapies.

The active substance, maribavir, is an antiviral that competitively inhibits the protein kinase activity of human cytomegalovirus (HCMV) enzyme unique long (UL) 97 at low concentrations, thereby suppressing protein phosphorylation essential for viral replication.

Livtencity is available as a film-coated tablet containing 200 mg of maribavir. Other ingredients in the core tablet are microcrystalline cellulose, sodium starch glycolate and magnesium stearate. Ingredients in the film coating include polyvinyl alcohol, macrogol (i.e., polyethylene glycol), titanium dioxide, talc, brilliant blue FCF aluminium lake (FD&C Blue #1) and purified water.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, maribavir, is manufactured at Carbogen Amcis AG, Bubendorf, Switzerland. The drug product, Livtencity Film-coated Tablet 200 mg, is manufactured at Catalent CTS, LLC, Kansas City, USA.

Drug substance:

Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP).

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in accordance with ICH Q3A and Q3C guidelines.

The drug substance specifications are established in accordance with ICH Q6A guideline, and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is double low-density polyethylene (LDPE) bag sealed with a plastic tie, placed in high-density polyethylene (HDPE) containers. The stability data presented was adequate to support the storage of the drug substance at 25ºC with a re-test period of 60 months.

Drug product:

The Livtencity tablets are manufactured using a dry blending, lubrication and direct compression approach followed by film-coating which is considered a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A guideline, and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is a HDPE bottle containing 28 or 56 tablets. The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at or below 30ºC.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of maribavir in the treatment of post-transplant CMV infection and disease was based primarily on one pivotal Phase III study (SHP620-303), referred to as Study 303. This was a multicentre, open-label, randomised study of maribavir compared with investigator-assigned anti-CMV treatment (IAT) in haematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) recipients with CMV infection refractory to the most recently administered anti-CMV treatment agents, including ganciclovir, valganciclovir, foscarnet, and/or cidofovir. Additionally, patients may have one or more resistance-associated amino acid substitutions (RASs) conferring resistance to ganciclovir, valganciclovir, foscarnet, and/or cidofovir. The open-label study design, while having inherent limitations, was considered appropriate to allow physicians to customise treatment for each patient and with the use of laboratory-confirmed CMV clearance as the primary endpoint.

Patients in the study were randomised in a 2:1 ratio to receive either oral maribavir 400 mg twice daily or IAT for a total of 8 weeks. IAT included ganciclovir, valganciclovir, foscarnet, or cidofovir, administered as mono- or dual-therapy. Following a three-week treatment period, subjects in the IAT group were eligible for maribavir rescue therapy if they exhibited increased CMV viraemia, persistent CMV disease or treatment intolerance. The active comparators in the IAT group are agents with established local use for the treatment of CMV disease. The inclusion of these agents in the IAT group as active comparators was considered acceptable.

The primary efficacy endpoint was confirmed clearance of CMV viraemia at the end of study Week 8, defined as plasma CMV DNA concentrations below the lower limit of quantification (<LLOQ, i.e., <137 IU/mL) in 2 consecutive post-baseline samples separated by at least 5 days. This endpoint was assessed regardless of whether study-assigned treatment was discontinued before the end of stipulated 8 weeks of therapy. The key secondary endpoint was achievement of CMV viraemia clearance and symptom control at the end of study Week 8, followed by maintenance of this treatment effect through Week 16. Symptom control was defined as resolution or improvement of tissue-invasive CMV disease or CMV syndrome for subjects symptomatic at baseline, or no new symptoms of tissue-invasive CMV disease or CMV syndrome for subjects asymptomatic at baseline. To control for Type 1 error, a fixed sequence testing procedure was used to manage multiple comparisons in the hypothesis testing of the primary and key secondary endpoints. The key secondary endpoint, assessing sustained CMV clearance and symptom improvement from Week 8 through Week 16, was only tested if the primary endpoint comparison showed statistical significance.

A total of 352 patients were randomised in the study and were included in the randomised set: 235 patients in the maribavir group and 117 patients in the IAT group. The median age was 57 years (range 19 to 79 years) in the maribavir group and 54 years (range 19 to 77 years) in the IAT group. The study population was predominantly white (75.6%). The maribavir group had a higher proportion of patients ≥65 years of age compared with IAT (23.0% and 13.7%, respectively), as well as a higher proportion of male patients (63.0% and 55.6%, respectively). Most patients in the control group received monotherapy with either ganciclovir/valganciclovir (48.3%) or foscarnet (40.5%) as the IAT. Overall, 77.9% in the maribavir group and 31.6% in the IAT group completed 8 weeks of study-assigned treatment. Treatment discontinuation due to adverse events (AEs) was nearly 5-fold higher for the IAT group than for maribavir-treated patients (30.8% vs 6.4%, respectively).

The majority of patients meeting virologic inclusion criteria fell into the category of low CMV DNA viral load (<9100 IU/mL) (67.6%), while only 6.0% had viral load categorised as high (≥91000 IU/mL). More than half of the patients harboured virus with at least one resistance-associated amino acid substitution (RAS) conferring resistance to ganciclovir, foscarnet, and/or cidofovir, with a higher proportion in the IAT group (59.5%) compared to the maribavir group (51.7%). Importantly, 57.1% of patients with baseline RAS known to confer resistance to ganciclovir/valganciclovir received these agents as IAT, indicating treatment with agents to which their virus was already resistant. While these imbalances may favour the maribavir group, they reflect real-world practice where treatment options for CMV infections are limited and often associated with significant toxicities.

The study achieved its primary efficacy endpoint, demonstrating that 55.7% of maribavir patients achieved confirmed CMV viraemia clearance at Week 8, compared to 23.9% of IAT patients (adjusted difference: 32.8%, 95% CI: 22.80 to 42.74, p<0.001). Multiple sensitivity analyses were conducted, with most maintaining statistical significance. However, the completers analysis, which included only patients who finished the full 8-week randomised treatment (183 out of 235 maribavir vs 37 out of 117 IAT patients), showed a smaller, non-significant difference favouring maribavir (70.5% vs 59.5%, p=0.25). Notably, when investigating reasons for failing to achieve the primary endpoint, virologic non-response rates at Week 8 were similar between groups (maribavir: 36%, IAT: 34%). This suggests that the apparent treatment effect favouring maribavir might be attributable to a higher proportion of IAT patients failing due to drug or study discontinuation (maribavir: 9%, IAT: 38%)—primarily from adverse events—rather than differences in antiviral efficacy.

The key secondary endpoint also showed favourable results for maribavir. The composite outcome of viraemia clearance and CMV infection symptom control at Week 8, maintained through Week 16, was achieved by 18.7% of maribavir patients vs 10.3% of IAT patients (adjusted difference: 9.5%, 95% CI: 2.02 to 16.88, p=0.013).

Summary of key efficacy results

	IAT (N=117) n (%)	**Maribavir 400 mg BID (N=235) n (%)**
Primary endpoint		
CMV Viraemia Clearance Response		
Responders	28 (23.9)	131 (55.7)
Adjusted difference in proportion of responders (95% CI)[a]	32.8 (22.80, 42.74)	
p-value: adjusted[a]	<0.001	
Key secondary endpoint		

CMV Viraemia Clearance and CMV Infection Symptom Control Response		
Responders	12 (10.3)	44 (18.7)
Adjusted difference in proportion of responders (95% CI)[a]	9.5 (2.02, 16.88)	
p-value: adjusted[a]	0.013	

BID=twice daily; CI=confidence interval; CMV=cytomegalovirus; DNA=deoxyribonucleic acid; IAT=investigator-assigned anti-CMV treatment; N=number of subjects

[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration if homogeneity was met. The minimum risk weight method was used if the homogeneity was not met. Only those with both stratification factors were included in the computation.

Overall, the results from Study 303 demonstrated efficacy of maribavir in treating adults with post-transplant CMV infection and disease who are refractory (with or without resistance) or intolerant to prior therapies. While the superior outcomes in the maribavir group appear to be driven partly by better tolerability and lower discontinuation rates rather than superior antiviral efficacy, the totality of evidence supported clinically meaningful benefit in this difficult-to-treat population with limited therapeutic options.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of maribavir was derived from the pivotal Phase III Study 303, comprising a total of 350 patients who received at least one dose of study treatment: 234 patients in the maribavir group and 116 patients in the IAT group. In Study 303, patients in the maribavir group were exposed to the study drug for a longer duration as compared to patients in the IAT group. The mean (SD) exposure duration was 52.5 (11.81) days in the maribavir group and 36.0 (18.06) days in the IAT group. Analysis of actual exposure days (defined as days where at least one dose was taken) demonstrated a mean (SD) of 48.6 (13.82) days in the maribavir group and 31.2 (16.91) days in the IAT group. This difference in exposure should be considered when comparing the incidence of AEs in the 2 treatment groups.

Overview of safety profile (Study 303)

AE	Maribavir 400 mg BID (N=234)	IAT (N=116)
Any AE	228 (97.4%)	106 (91.4%)
Treatment-related AE	141 (60.3%)	57 (49.1%)
SAE	90 (38.5%)	43 (37.1%)
Treatment-related SAE	12 (5.1%)	17 (14.7%)
Discontinuations due to AE	31 (13.2%)	37 (31.9%)
Deaths due to AE	16 (6.8%)	6 (5.2%)

A total of 97.4% of patients in the maribavir group and 91.4% in the IAT group experienced at least one AE. The high incidence in both groups reflected the expected rates in a post-transplant population, with higher incidences in the treatment arm which might be attributed to the longer treatment duration. The most frequently reported AEs (≥10%) were dysgeusia (37.2% vs 3.4% in maribavir vs IAT groups), neutropenia (9.4% vs 22.4%), nausea (21.4% vs 21.6%), diarrhoea (18.8% vs 20.7%), vomiting (14.1% vs 16.4%), pyrexia (10.3% vs 14.7%), headache (8.1% vs 12.9%), anaemia (12.4% vs 12.1%), fatigue (12.0% vs 8.6%), and CMV viraemia (10.3% vs 5.2%). Notably, neutropenia occurred less frequently with maribavir (9.4%) compared to IAT (22.4%), predominantly affecting patients receiving ganciclovir/valganciclovir (33.9%). Acute kidney injury was most common in the foscarnet group (21.3%), consistent with its known safety profile.

Treatment-related AEs occurred more frequently in maribavir-treated patients (60.3%) than IAT patients (49.1%), primarily due to dysgeusia (35.9% vs 0.9%) and taste disorder (8.5% vs 0.9%). Other common treatment-related AEs in the maribavir group were neutropenia (1.7% vs 13.8% in maribavir vs IAT groups), nausea (8.5% vs 9.5%), acute kidney injury (1.7% vs 7.8%), vomiting (7.7% vs 4.3%), anaemia (1.3% vs 7.8%), immunosuppressant drug level increased (6.0% vs 0%), thrombocytopenia (0% vs 5.2%), and diarrhoea (3.8% vs 5.2%).

The incidence of serious AEs (SAEs) was comparable between groups (38.5% vs 37.1%). Infections and infestations were the most common SAEs (22.6% vs 14.7%), with the higher maribavir rate likely due to longer treatment duration, as evidenced by similar 28-day rates (11.1% vs 9.5%). Treatment-related SAEs were less frequent with maribavir (5.1%) than IAT (14.7%), with the difference largely due to neutropenia and febrile neutropenia in ganciclovir/valganciclovir-treated patients.

Treatment discontinuation due to AEs occurred at a lower rate in the maribavir group (13.2%) compared with the IAT group (31.9%). In the maribavir group, infections and infestations constituted the predominant cause of discontinuation (7.3% for maribavir vs 6.9% for IAT); whereas in the IAT group, discontinuations were primarily attributed to blood and lymphatic system disorders (11.2%) and renal and urinary disorders (9.5%).

Fatal SAEs occurred at comparable rates between the maribavir (6.8%) and IAT (5.2%) groups. One treatment-related fatal SAE was reported in the maribavir group. This was a case of sudden cardiac death, which was initially attributed to maribavir due to potential drug interactions, but was more likely to be due to an interaction between concomitant domperidone and posaconazole that the patient was on, causing prolonged QTc and sudden cardiac death.

The most frequently reported AESIs (≥10%) were taste disturbance (46.2% vs 4.3% in maribavir vs IAT groups), gastrointestinal disorders (nausea, vomiting, diarrhoea) (33.3% vs 37.9%), invasive fungal or bacterial or viral infections (23.5% vs 19.0%), neutropenia (10.3% vs 25.9%), and graft-versus-host disease (GVHD) (9.0% vs 4.3%). Treatment-related taste disturbance was observed in 44.0% of patients receiving maribavir therapy, in contrast to 1.7% in the IAT group. Among these cases, treatment discontinuation due to taste disturbance occurred in only 2 patients (0.9%). Overall, the incidences of treatment-related gastrointestinal AEs, including nausea, diarrhoea and vomiting were comparable between the maribavir and IAT groups (12.8% vs 11.2%). None of the observed invasive fungal, bacterial or viral infections were assessed to be treatment-related. Relevant safety information on taste disturbance as well as very common occurrences of gastrointestinal AEs have been included in the package insert.

The safety profile of maribavir is characterised primarily by gastrointestinal AEs which could be managed through appropriate clinical interventions such as symptomatic treatment and supportive care. Overall, discontinuation rates were significantly lower compared with conventional anti-CMV treatments.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for post-transplant CMV infection involves empiric use of available anti-CMV agents such as ganciclovir, valganciclovir, foscarnet, and cidofovir. The use of these agents is limited by their respective toxicity profiles and the development of resistance. Patients

whose disease is resistant/refractory after treatment with first-line anti-CMV agents have limited treatment options.

In the pivotal Phase III Study 303, the results demonstrated that 55.7% of maribavir-treated patients compared with 23.9% in the IAT group achieved the primary endpoint of confirmed clearance of plasma CMV DNA at study Week 8. The difference in proportion of responders between treatment groups was statistically significant in favour of maribavir (32.8%, 95% CI: 22.80 to 42.74, $p<0.001$). While multiple sensitivity analyses confirmed the robustness of these results, the completers analysis, comprising only patients who completed the full 8-week randomised treatment, showed a numerical advantage for maribavir that did not reach statistical significance. The key secondary endpoint aligned with the primary outcome, demonstrating favourable results for maribavir.

In terms of safety, the predominant AEs with maribavir treatment were dysgeusia and gastrointestinal effects, most being mild to moderate in severity. Maribavir demonstrated a more favourable profile regarding bone marrow suppression and nephrotoxicity compared with IAT agents. The most frequent AESIs in the maribavir group included taste disturbance, gastrointestinal disorders (nausea, vomiting, diarrhoea), and invasive fungal, bacterial, or viral infections. Treatment-related taste disturbance occurred in 44.0% of maribavir-treated patients versus 1.7% in the IAT group, there were 2 patients (0.9%) in the maribavir group discontinued treatment due to this AE. Despite longer treatment duration in the maribavir group, gastrointestinal AEs remained comparable between groups, with treatment-related nausea, diarrhoea, and vomiting reported in 12.8% of maribavir recipients versus 11.2% of IAT patients. No causal relationship was established between maribavir treatment and any invasive infections.

Overall, the benefit-risk profile of maribavir for the treatment of adults with post-transplant CMV infection/disease who are refractory or intolerant to one or more prior therapies was considered to be favourable since efficacy was demonstrated and the safety profile was manageable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Livtencity for the treatment of adults with post-transplant CMV infection/disease who are refractory (with or without genotypic resistance) or intolerant to one or more prior therapies was deemed positive and approval of the product registration was granted on 18 March 2025.

APPROVED PACKAGE INSERT AT REGISTRATION

1. Name of the Medicinal Product

LIVTENCITY (maribavir)

2. Qualitative and Quantitative Composition

LIVTENCITY is available in 200 mg immediate-release tablets and is intended for oral administration. Each film-coated tablet contains 200 mg of maribavir, a potent, selective, antiviral drug belonging to the benzimidazole ribosides class.
For excipients, see section 6.1.

3. Pharmaceutical Form

Dosage Form:

Available Pharmaceutical Form	Strength	Color	Shape	Markings
Film-coated tablet	200 mg	Blue	Oval shaped convex	The film-coated tablets are debossed with "SHP" on one side and "620" on the other side

4. Clinical Particulars

4.1 Therapeutic Indications

Treatment of adults with post-transplant cytomegalovirus (CMV) infection/disease, who are refractory (with or without genotypic resistance) or intolerant to one or more prior therapies (see 4.3 CONTRAINDICATIONS, 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and 5.1 PHARMACODYNAMIC PROPERTIES).

4.2 Posology and Method of Administration

Posology

Therapeutic Indications	Posology
Treatment of adults with post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies.	400 mg (two 200 mg tablets) twice daily resulting in a daily dose of 800 mg.

Treatment duration may need to be individualized based on the clinical characteristics of each patient.

In Study 303, 400 mg (two 200 mg tablets) twice daily of LIVTENCITY was administered for 8 weeks. LIVTENCITY doses up to 1200 mg twice daily were well tolerated for up to 24 weeks in Phase 2 studies *(see Pharmacodynamic Properties, 5.1)*.

Dosage Adjustment

Dosage Adjustment When Co-administered with Anticonvulsants

If LIVTENCITY is co-administered with carbamazepine, increase the dosage of LIVTENCITY to 800 mg twice daily *(see Interaction with Other Medications and Other Forms of Interaction, 4.5).*

If LIVTENCITY is co-administered with phenytoin or phenobarbital, increase the dosage of LIVTENCITY to 1,200 mg twice daily *(see Interaction with Other Medications and Other Forms of Interaction, 4.5).*

Special Patient Populations

Elderly Patients

No dose adjustment is required for patients over 65 years of age.

Pediatric Patients

The safety and efficacy of LIVTENCITY in patients below 18 years of age have not been established.

Impaired Renal Function

No dose adjustment of LIVTENCITY is needed for patients with mild, moderate, or severe renal impairment. Administration of LIVTENCITY in patients with end stage renal disease (ESRD), including patients on dialysis, has not been studied *(see Pharmacokinetic Properties, 5.2).*

Impaired Hepatic Function

No dose adjustment of LIVTENCITY is needed for patients with mild (Child-Pugh Class A) or moderate hepatic impairment (Child-Pugh Class B). Administration of LIVTENCITY in

patients with severe hepatic impairment (Child-Pugh Class C) has not been studied *(see Pharmacokinetic Properties, 5.2).*

Method of Administration

LIVTENCITY is intended for oral use only and can be taken with or without food. The immediate-release tablet can be taken as a whole, dispersed, or crushed tablets by mouth, or as dispersed tablets through nasogastric or orogastric tube.

4.3 Contraindications

LIVTENCITY is contraindicated in individuals with known hypersensitivity to LIVTENCITY or any components of the formulation.

Coadministration of LIVTENCITY with ganciclovir or valganciclovir is contraindicated. LIVTENCITY may antagonize the antiviral effect of ganciclovir and valganciclovir by inhibiting human CMV UL97 serine/threonine kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir *(see Interaction with Other Medications and Other Forms of Interaction, 4.5 and Pharmacokinetic Properties, 5.2).*

4.4 Special Warnings and Special Precautions for Use

Patients with CMV Central Nervous System (CNS) Infection

LIVTENCITY was not studied in patients with CMV CNS infection. Based on nonclinical data, maribavir may cross the blood-brain barrier in humans, but, CNS penetration is expected to be low compared to plasma levels *(see Pharmacokinetic Properties 5.2 and Nonclinical Safety Data, 5.3)*. Therefore, LIVTENCITY is not expected to be effective in treating CMV CNS infections (e.g., meningo-encephalitis).

Virologic Failure During Treatment and Relapse Post-Treatment

Virologic failure can occur during and after treatment with LIVTENCITY. Virologic relapse during the post-treatment period usually occurred within 4-8 weeks after treatment discontinuation. Monitor CMV DNA levels and check for resistance if patient does not respond to treatment. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir *(see Pharmacodynamic Properties, 5.1)*.

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Medicinal Product Interactions

The concomitant use of LIVTENCITY and certain medicinal products may result in known or potentially significant medicinal product interactions, some of which may lead to:

- possible clinically significant adverse reactions from greater exposure of concomitant medicinal products
- reduced therapeutic effect of LIVTENCITY.

See Table 1 for steps to prevent or manage these known or potentially significant medicinal product interactions, including dosing recommendations *(see Contraindications, 4.3 and Interaction with Other Medications and Other Forms of Interaction, 4.5)*.

Use With Immunosuppressant Drugs

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are cytochrome P450 (CYP)3A/P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporine, sirolimus, and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY and adjust the dose, as needed *(see Interaction with Other Medications and Other Forms of Interaction, 4.5, Undesirable Effects, 4.8 and Pharmacokinetic Properties, 5.2).*

4.5 Interaction with Other Medications and Other Forms of Interaction

Effect of Other Medicinal Products on LIVTENCITY

Maribavir is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of maribavir *(see Pharmacokinetic Properties, 5.2)*. Concomitant administration of strong CYP3A inducers, such as rifampicin, rifabutin, and St John's wort, should be avoided, as significant decreases in maribavir plasma concentrations may occur which may result in decrease in efficacy. Alternative antimicrobial or anti-tuberculosis therapy with a lower CYP3A induction potential should be considered *(see Pharmacokinetic Properties, 5.2)*.

Coadministration with carbamazepine, phenobarbital, and phenytoin (strong or moderate CYP3A inducers) is likely to decrease maribavir concentrations, and therefore, the LIVTENCITY dose should be increased according to Table 1 *(see Posology and Method of Administration, 4.2 and Pharmacokinetic Properties, 5.2)*.

Coadministration of LIVTENCITY with other strong or moderate CYP3A inducers has not been evaluated, but decreased maribavir concentrations are expected. If coadministration with other strong or moderate CYP3A inducers cannot be avoided, a LIVTENCITY dose increase up to 1200 mg twice daily should be considered *(see Posology and Method of Administration, 4.2 and Pharmacokinetic Properties, 5.2)*.

Coadministration of LIVTENCITY and medicinal products that are inhibitors of CYP3A may result in increased plasma concentrations of maribavir *(see Pharmacokinetic Properties, 5.2)*. However, no dose adjustment is needed when maribavir is co-administered with CYP3A inhibitors.

Effect of LIVTENCITY on Other Medicinal Products

LIVTENCITY is contraindicated with valganciclovir/ganciclovir. LIVTENCITY may antagonize the antiviral effect of ganciclovir and valganciclovir by inhibiting human CMV UL97 serine/threonine kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir *(see Contraindications, 4.3 and Pharmacodynamic Properties, 5.1).*

At therapeutic concentrations, clinically significant interactions are not expected when LIVTENCITY is coadministered with substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 2D6, and 3A4; UGT1A1, 1A4, 1A6, 1A9, 2B7; P-gp (except for sensitive P-gp substrates with narrow therapeutic window); bile salt export pump (BSEP); multidrug and toxin extrusion protein (MATE)1/2K; organic anion transporters (OAT)1 and OAT3; organic cation transporters (OCT)1 and OCT2; organic anion transporting polypeptide (OATP)1B1 and OATP1B3 based on *in vitro* and clinical drug interaction results *(see* Table 1 *and Pharmacokinetic Properties, 5.2)* except the following medicinal products.

Coadministration of LIVTENCITY increased plasma concentrations of immunosuppressants, including tacrolimus (see Table 1). When the immunosuppressants tacrolimus, cyclosporine, everolimus, or sirolimus are coadministered with LIVTENCITY, frequently monitor

immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY and adjust dose, as needed *(see Special Warnings and Special Precautions for Use, 4.4 and* Table 1*)*.

Coadministration of LIVTENCITY with rosuvastatin, a sensitive BCRP substrate, is expected to increase rosuvastatin concentration. Rosuvastatin is associated with the occurrence of myopathy and rhabdomyolysis *(see Special Warnings and Special Precautions for Use, 4.4 and* Table 1*)*. Maribavir inhibited P-gp transporter in vitro at clinically relevant concentrations. In a clinical study, co-administration of LIVTENCITY increased plasma concentrations of digoxin (see Table 1). Therefore, caution should be exercised when LIVTENCITY and sensitive P-gp substrates (e.g., digoxin) are co-administered. Serum digoxin concentrations should be monitored, and dose of digoxin may need to be reduced, as needed (see Table 1).

General Information

If dose adjustments of concomitant medicinal products are made due to treatment with LIVTENCITY, doses should be readjusted after treatment with LIVTENCITY is completed. Table 1 provides a listing of established or potentially clinically significant medicinal product interactions. The medicinal product interactions described are based on studies conducted with LIVTENCITY or are predicted medicinal product interactions that may occur with LIVTENCITY *(see Special Warnings and Special Precautions for Use, 4.4 and Pharmacokinetic Properties, 5.2)*.

Table 1: Interactions and Dose Recommendations with Other Medicinal Products

Medicinal Product by Therapeutic Area	**Effect on Geometric Mean Ratio (90 % CI) (likely mechanism of action)**	**Recommendation Concerning Coadministration with maribavir**
Acid-Reducing Agents		
antacid (aluminium and magnesium hydroxide oral suspension) (20 mL single dose, maribavir 100 mg single dose)	↔ maribavir AUC 0.89 (0.83, 0.96) C_{max} 0.84 (0.75, 0.94)	No dose adjustment is required.
famotidine	Interaction not studied. Expected: ↔ maribavir	No dose adjustment is required.

omeprazole	↔ maribavir ↑ plasma omeprazole/5-hydroxyomeprazole concentration ratio 1.71 (1.51, 1.92) (CYP2C19 inhibition)	No dose adjustment is required.
pantoprazole	Interaction not studied. Expected: ↔ maribavir	No dose adjustment is required.
Antiarrhythmics		
digoxin (0.5 mg single dose, 400 mg twice daily maribavir)	↔ digoxin AUC 1.21 (1.10, 1.32) C_{max} 1.25 (1.13, 1.38) (P-gp inhibition)	Use caution when maribavir and digoxin are coadministered. Monitor serum digoxin concentrations. The dose of digoxin may need to be reduced when coadministered with maribavir
Antibiotics		
erythromycin	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Anticonvulsants		
carbamazepine	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to 800 mg BID is recommended when coadministration with carbamazepine.
phenobarbital	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to1200 mg BID is recommended when coadministration with phenobarbital.
phenytoin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to 1200 mg BID is recommended when coadministration with phenytoin.
Anti-inflammatories		
Medicinal Product by Therapeutic Area	**Effect on Geometric Mean Ratio (90 % CI) (likely mechanism of action)**	**Recommendation Concerning Coadministration with maribavir**
sulfasalazine	Interaction not studied. Expected: ↑ sulfasalazine (BCRP inhibition)	No dose adjustment is required.
Antifungals		
ketoconazole (400 mg single dose, maribavir 400 mg single dose)	↑ maribavir AUC 1.53 (1.44, 1.63) C_{max} 1.10 (1.01, 1.19) (CYP3A inhibition)	No dose adjustment is required.
voriconazole	Expected:	No dose adjustment is required.

(200 mg twice daily, maribavir 400 mg twice daily)	↑ maribavir (CYP3A inhibition) ↔ voriconazole AUC 0.93 (0.83, 1.05) C_{max} 1.00 (0.87, 1.15) (CYP2C19 inhibition)	
Antihypertensives		
diltiazem	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Antimycobacterials		
rifabutin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Coadministration of maribavir and rifabutin is not recommended due to potential for a decrease in efficacy of maribavir.
rifampin (600 mg once daily, maribavir 400 mg twice daily)	↓ maribavir AUC 0.40 (0.36, 0.44) C_{max} 0.61 (0.52, 0.72) C_{trough} 0.18 (0.14, 0.25) (CYP3A and CYP1A2 induction)	Coadministration of maribavir and rifampin is not recommended due to potential for a decrease in efficacy of maribavir.
Antitussives		
dextromethorphan (30 mg single dose, maribavir 400 mg twice daily)	↔ dextrorphan AUC 0.97 (0.94, 1.00) C_{max} 0.94 (0.88, 1.01) (CYP2D6 inhibition)	No dose adjustment is required.
CNS Stimulants		
Herbal Products		
St. John's wort (Hypericum perforatum)	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Coadministration of maribavir and St. John's wort is not recommended due to potential for a decrease in efficacy of maribavir.
HMG-CoA Reductase Inhibitors		
Medicinal Product by Therapeutic Area	**Effect on Geometric Mean Ratio (90 % CI) (likely mechanism of action)**	**Recommendation Concerning Coadministration with maribavir**
atorvastatin fluvastatin simvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (BCRP inhibition)	No dose adjustment is required.
rosuvastatin[a]	Interaction not studied. Expected: ↑ rosuvastatin (BCRP inhibition)	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis.
Immunosuppressants		

cyclosporine[a] everolimus[a] sirolimus[a]	Interaction not studied. Expected: ↑ cyclosporine, everolimus, sirolimus (CYP3A/P-gp inhibition)	Frequently monitor cyclosporine, everolimus and sirolimus levels, especially following initiation and after discontinuation of LIVTENCITY and adjust dose, as needed.
tacrolimus[a]	↑ tacrolimus AUC 1.51 (1.39, 1.65) C_{max} 1.38 (1.20, 1.57) C_{trough} 1.57 (1.41, 1.74) (CYP3A/P-gp inhibition)	Frequently monitor tacrolimus levels, especially following initiation and after discontinuation of LIVTENCITY and adjust dose, as needed.
Oral Anticoagulants		
warfarin (10 mg single dose, maribavir 400 mg twice daily)	↔ S-warfarin AUC 1.01 (0.95, 1.07) (CYP2C9 inhibition)	No dose adjustment is required.
Oral Contraceptives		
systemically acting oral contraceptive steroids	Interaction not studied. Expected: ↔ oral contraceptive steroids (CYP3A inhibition)	No dose adjustment is required.
Sedatives		
Midazolam (0.075 mg/kg single oral dose, maribavir 400 mg twice daily)	↔ midazolam AUC 0.89 (0.79, 1.00) C_{max} 0.82 (0.70, 0.96)	No dose adjustment is required.

↑ = increase, ↓ = decrease, ↔ = no change
CI = Confidence Interval; SD = Single Dose; QD = Once Daily; BID = Twice Daily
*AUC0-∞ for single dose, AUC0-12 for twice daily dose daily.
Note: the table is not extensive but provides examples of clinically relevant interactions.
[a] Refer to the respective prescribing information.

4.6 Pregnancy, Lactation and Fertility

Pregnancy

There is no clinical experience with LIVTENCITY in pregnant women. Studies in animals have shown reproductive toxicity *(see Nonclinical Safety Data, 5.3)*. LIVTENCITY is not recommended during pregnancy and in women of childbearing potential not using contraception *(see Nonclinical Safety Data, 5.3).*

Lactation

It is unknown whether maribavir or its metabolites are excreted in human milk. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with LIVTENCITY.

Fertility

Fertility studies were not conducted in humans with LIVTENCITY. No effects on fertility or reproductive performance were noted in rats in a combined fertility and embryofetal development study, however, a decrease in sperm straight-line velocity was observed at doses ≥ 100 mg/kg/day (which is estimated to be less than the human exposure at the RHD). There were no effects on reproductive organs in either males or females in nonclinical studies in rats and monkeys *(see Nonclinical Safety Data, 5.3).*

4.7 Effects on Ability to Drive and Use Machines

LIVTENCITY has no influence on the ability to drive and use machines. LIVTENCITY may cross the blood-brain barrier in humans, but CNS penetration is expected to be low compared to plasma levels.

4.8 Undesirable Effects

Clinical Trials

The safety of LIVTENCITY was evaluated in Study 303 in which 352 patients were randomised and treated with LIVTENCITY (N=234) or Investigator Assigned Treatment (IAT) consisting of monotherapy or dual therapy with ganciclovir, valganciclovir, foscarnet, or cidofovir (N=117) for an 8 week treatment phase following a diagnosis of resistant/refractory CMV. Adverse events were collected during the treatment phase and follow-up phase through

Study Week 20. The mean exposures (SD) for LIVTENCITY was 48.6 (13.82) days. LIVTENCITY-treated patients received treatment a maximum of 60 days.

The most commonly reported adverse reactions occurring in at least 10% of subjects in the LIVTENCITY group were: taste disturbance (46%), nausea (21%), diarrhoea (19%), vomiting (14%), and fatigue (12%). The most commonly reported serious adverse reactions were diarrhoea (2%), and nausea, weight decreased, fatigue, immunosuppressant drug level increased, and vomiting occurring at < 1%.

Treatment-emergent serious adverse events (SAEs) considered related to study-assigned treatment occurred less frequently in the LIVTENCITY group than in the IAT group (5.1% and 14.7%, respectively). No patients in the LIVTENCITY group experienced serious, drug- related neutropenia or febrile neutropenia. In contrast in patients treated with ganciclovir/valganciclovir, 4% of patients had serious related neutropenia and 7% had serious related febrile neutropenia, In addition, 1% of patients in the LIVTENCITY group and 11% in the foscarnet group experienced serious related renal disorders (acute kidney injury and renal impairment).

The following convention is used for the classification of the frequency of an adverse drug reaction (ADR) and is based on the Council for International Organizations of Medical Sciences (CIOMS) guidelines: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000).

Table 2: Adverse Drug Reactions Associated with < LIVTENCITY>

System Organ Class	Frequency	Adverse reactions
Gastrointestinal disorders	Very Common	Diarrhea, Nausea, Vomiting
	Common	Abdominal pain upper
General disorders and administration site conditions	Very common	Fatigue
	Common	Decreased appetite
Investigations	Common	Immunosuppressant drug level increaseda, Weight decreased
Nervous system disorders	Very common	Taste disturbance[b]
	Common	Headache

[a] Immunosuppressant drug level increased includes the following reported preferred terms: immunosuppressant drug level increased and drug level increased.

[b] Taste disturbance includes the following reported preferred terms: ageusia, dysgeusia, hypogeusia and taste disorder.

Description of Selected Adverse Reactions

Taste Disturbance

Taste disturbance (comprising the reported preferred terms ageusia, dysgeusia, hypogeusia, and taste disorder) occurred in 46% of patients treated with LIVTENCITY. These events rarely led to discontinuation of LIVTENCITY (0.9%) and resolved either while patients remained on therapy (37%) or within a median of 7 days (Kaplan-Meier estimate, 95% CI: 4-8 days) after treatment discontinuation

Immunosuppressant Drug Level Increase

Immunosuppressant drug level increase was reported as an adverse event in 9% of patients treated with LIVTENCITY.

LIVTENCITY has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A/ P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporine, sirolimus and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY and adjust the dose, as needed *(see Special Warnings and Special Precautions for Use, 4.4, Interactions with Other Medications and Other Forms of Interaction, 4.5 and Pharmacokinetic Properties, 5.2)*.

4.9 Overdose

In Study 303, an accidental overdose of a single extra dose occurred in 1 LIVTENCITY-treated subject on Day 13 (1200 mg total daily dose). No adverse reactions were reported.

In Study 202, patients were treated with up to 1200 mg twice daily for up to 24 weeks of treatment. The safety profile of higher doses and longer durations were comparable to 400 mg twice daily. However, the highest dose was associated with a greater incidence of immunosuppressant drug level increased.

There is no known specific antidote for maribavir. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment instituted. Due to the high plasma protein binding of maribavir, dialysis is unlikely to reduce plasma concentrations of maribavir significantly.

4.10 Drug Abuse and Dependence

There is no evidence of drug abuse or dependence with LIVTENCITY use.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Mechanism of Action

The antiviral activity of maribavir is mediated by competitive inhibition of the protein kinase activity of HCMV enzyme UL97, which results in inhibition of the phosphorylation of proteins; an effect achieved at low concentrations of maribavir.

Antiviral Activity

Maribavir selectively inhibited in vitro HCMV replication in yield reduction, DNA hybridization, and plaque reduction assays in human cell lines at noncytotoxic submicromolar concentrations. The EC_{50} values ranged from 0.03 to 2.2 μM depending on the cell line and assay endpoint.

The cell culture antiviral activity of maribavir has also been evaluated against CMV clinical isolates. The median EC_{50} values were 0.1 μM (n=10, range 0.03-0.13 μM) and 0.28 μM (n=10, range 0.12-0.56 μM) using DNA hybridization and plaque reduction assays, respectively.

Maribavir is highly selective for HCMV. There is no significant difference in baseline maribavir EC_{50} values across the four HCMV glycoprotein B genotypes.

Combination Antiviral Activity

When maribavir was tested in combination with other antiviral compounds, it showed additive interactions with letermovir, foscarnet, cidofovir, and GW275175X (a benzimidazole CMV terminase inhibitor) against wild-type and mutant HCMV, strong antagonism with ganciclovir, and strong synergy with the mechanistic target of rapamycin (mTOR) inhibitor sirolimus.

Viral Resistance

In Cell Culture

Maribavir does not affect the UL54-encoded DNA polymerase that, when presenting certain mutations, confers resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir. Mutations conferring resistance to maribavir have been identified on gene UL97: L337M,

F342Y, V353A, L397R, T409M, H411L/N/Y, and C480F. These mutations confer resistance that ranges from 3.5-fold to >200-fold increase in EC_{50} values. UL27 gene variants (R233S, W362R, W153R, L193F, A269T, V353E, L426F, E22stop, W362stop, 218delC, and 301-311del) conferred only mild maribavir resistance (<5-fold increase in EC_{50}).

In Clinical Studies

In Phase 2 Study 202 and Study 203 evaluating maribavir in 279 hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT) recipients, post-treatment pUL97 genotyping data from 23 of 29 patients who initially achieved viremia clearance and later experienced recurrent CMV infection while on maribavir, showed 17 patients with mutations T409M or H411Y and 6 patients with mutation C480F. Among 25 patients who did not respond to >14 days of maribavir therapy, 9 had mutations T409M or H411Y, and 5 patients had mutation C480F. Additional pUL27 genotyping was performed on 39 patients in Study 202 and 43 patients in Study 203. The only resistance-associated amino acid substitution in pUL27 that was not detected at baseline was G344D. Phenotypic analysis of pUL27 and pUL97 recombinants showed that pUL97 mutations T409M, H411Y, and C480F conferred 78-fold, 15-fold, and 224-fold increases, respectively, in maribavir EC_{50} compared with the wild-type strain. The pUL27 mutation G344D was not shown to confer maribavir resistance.

In Phase 3 Study 303, 60/234 patients (25.6%) were identified with treatment-emergent mutations in pUL97 that confer resistance to maribavir: C480F, F342Y, H411N, H411Y, T409M, F342Y+H411Y, F342Y+T409M+H411N, H411Y+C480F, T409M+C480F, T409M+H411Y, H411L+H411Y+C480F, H411N+C480F.

Cross Resistance

There is clinical evidence of cross-resistance to maribavir and ganciclovir/valganciclovir at UL97: F342Y- 4.5-fold and 6.0-fold increase in EC_{50} to maribavir and ganciclovir, respectively; and C480F- 224-fold and 2.3-fold increase in EC_{50} to maribavir and ganciclovir, respectively. The prevalence of F342Y, the only cross-resistant mutation present in Study 303 subjects prior to maribavir treatment, was low (3/309 subjects with baseline UL97 genotyping).

Pharmacodynamic Effects

Cardiac Electrophysiology

The effect of maribavir at doses up to 1200 mg on the QTc interval was evaluated in a randomised, single-dose, placebo-and active-controlled (moxifloxacin 400 mg oral) 4-period crossover thorough QT trial in 52 healthy subjects. Maribavir does not prolong QTc to any clinically relevant extent following the 1200 mg dose, with peak plasma concentrations approximately twice the steady-state peak concentration following 400 mg twice daily doses in transplant patients.

Clinical Studies

Treatment of adults with post-transplant CMV infection and/or disease, including those infections that were refractory and/or resistant to ganciclovir, valganciclovir, cidofovir, or foscarnet.

LIVTENCITY was evaluated in a Phase 3, multicenter, randomized, open-label, active-controlled superiority study (NCT02931539, Study 303) to assess the efficacy and safety of LIVTENCITY treatment compared to IAT in 352 HSCT and SOT recipients with CMV infections that were refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with or without confirmed resistance to 1 or more anti-CMV agents.

Patients were stratified by transplant type (HSCT or SOT) and screening viral load and then randomized in a 2:1 allocation ratio to receive LIVTENCITY 400 mg twice daily or IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) for an 8-week treatment period and a 12-week follow-up phase.

Table 3: Summary of the Demographic and Disease Characteristics of the Study Population in Study 303

Characteristic[a]	**IAT (N=117)**	**LIVTENCITY 400 mg Twice Daily (N=235)**
Age (years)[b]		
Median	54	57
Min, Max	19, 77	19, 79
Sex, n (%)		
Male	65 (56)	148 (63)
Female	52 (44)	87 (37)
Ethnicity, n (%)		
Hispanic or Latino	7 (6)	14 (6)
Not Hispanic or Latino	95 (81)	198 (84)
Not reported	12 (10)	19 (8)
Unknown	3 (3)	4 (2)
Race, n (%)		

White	87 (74)	179 (76)
Asian	7 (6)	9 (4)
Black or African American	18 (15)	29 (12)
Other	5 (4)	16 (7)
Missing	0	2 (1)
IAT treatment		
Foscarnet	47 (41)	n/a
Ganciclovir/ Valganciclovir	56 (48)	n/a
Cidofovir	6 (5)	n/a
Foscarnet+ Ganciclovir/Valganciclovir	7 (6)	n/a
Transplant type, n (%)		
HSCT	48 (41)	93 (40)
SOT[c]	69 (59)	142 (60)
Kidney[f]	32 (46)	74 (52)
Lung[f]	22 (32)	40 (28)
Heart[f]	9 (13)	14 (10)
Multiple[f]	5 (7)	5 (4)
Liver[f]	1 (1)	6 (4)
Pancreas[f]	0	2 (1)
Intestine[f]	0	1 (1)
CMV DNA levels category as reported by central laboratory, n (%)[d]		
High	7 (6)	14 (6)
Intermediate	25 (21)	68 (29)
Low	85 (73)	153 (65)
Baseline symptomatic CMV infection		
No	109 (93)	214 (91)
Yes[e]	8 (7)	21 (9)
CMV syndrome (SOT only), n (%)[e, f, g]	7 (88)	10 (48)
Tissue Invasive disease, n (%)[e, f, g]	1 (13)	12 (57)

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=hematopoietic stem cell transplant, IAT=investigator assigned anti-CMV treatment, max=maximum, min=minimum, N=number of patients, , n/a not applicable, SD=standard deviation, SOT=solid organ transplant

[a] Baseline was defined as the last value on or before the first dose date of study-assigned treatment, or date of randomization for patients who did not receive study-assigned treatment.

[b] Age was calculated as the difference between date of birth and date of informed consent, truncated to years.

[c] The most recent transplant

[d] Viral load was defined for analysis by the baseline central specialty laboratory plasma CMV DNA qPCR results as *high* (≥91,000 IU/mL), *intermediate* (≥9,100 and <91,000 IU/mL), and *low* (<9,100 IU/mL).

[e] Confirmed by Endpoint Adjudication Committee (EAC)

[f] Percentages are based on the number of patients within the category.

[g] Patients could have multiple reasons.

The primary efficacy endpoint was confirmed CMV viremia clearance (plasma CMV DNA concentration below the lower limit of quantification (<LLOQ; i.e., <137 IU/mL) as assessed by COBAS® AmpliPrep/COBAS® TaqMan® CMV test) at Week 8. The key secondary endpoint was CMV viremia clearance and CMV infection symptom control at the end of Study Week 8 with maintenance of this treatment effect through Study Week 16.

For the primary endpoint, LIVTENCITY was superior to IAT (56% vs. 24%, respectively). For the key secondary endpoint, 19% v. 10% achieved both CMV viremia clearance and CMV

infection symptom control in the LIVTENCITY and IAT group, respectively (see Table 4).

Table 4: Primary and Key Secondary Efficacy Endpoint Analysis (Randomized Set) in Study 303

	IAT (N=117) n (%)	LIVTENCITY 400 mg Twice Daily (N=235) n (%)
Primary Endpoint: CMV Viremia Clearance Response at Week 8		
Overall		
Responders	28 (24)	131 (56)
Adjusted difference in proportion of responders (95% CI)[a]		32.8 (22.8, 42.7)
p-value: adjusted[a]		<0.001
Key Secondary Endpoint: Achievement of CMV Viremia Clearance and CMV Infection Symptom Control[b] at Week 8, With Maintenance Through Week 16[b]		
Overall		
Responders	12 (10)	44 (19)
Adjusted difference in proportion of responders (95% CI)[a]		9.45 (2.0, 16.9)
p-value: adjusted[a]		0.013

CI=confidence interval; CMV=cytomegalovirus; HSCT=hematopoietic stem cell transplant; IAT=investigator-assigned anti-CMV treatment; N=number of patients; SOT=solid organ transplant.
[a] Cochran-Mantel-Haenszel weighted average approach was used for the adjusted difference in proportion (maribavir – IAT), the corresponding 95% CI, and the p-value after adjusting for the transplant type and baseline plasma CMV DNA concentration. Only those with both stratification factors were included in the computation.
[b] CMV infection symptom control was defined as resolution or improvement of tissue-invasive disease or CMV syndrome for symptomatic patients at baseline, or no new symptoms for patients who were asymptomatic at baseline.

The reasons for failure of the primary efficacy endpoint in Study 303 are summarized in Table 5:

Table 5: Analysis of Failures for Primary Efficacy Endpoint

Outcome at Week 8	**LIVTENCITY N=235 n (%)**	**IAT N=117 n (%)**
Responders (Confirmed DNA Level < LLOQ)[a]	**131 (56)**	**28 (24)**
Non-responders:	**104 (44)**	**89 (76)**
Due to virologic failure[b]:	**80 (34)**	**42 (36)**
• CMV DNA never < LLOQ	48 (20)	35 (30)
• CMV DNA breakthrough[b]	32 (14)	7 (6)
Due to drug/study discontinuation:	**21 (9)**	**44 (38)**
• Adverse events	8 (3)	26 (22)
• Deaths	10 (4)	3 (3)
• Withdrawal of consent	1 (<1)	9 (8)
• Other reasons[c]	2 (1)	6 (5)
Due to other reasons but remained on study[d]	**3 (1)**	**3 (3)**

CMV=Cytomegalovirus, IAT=Investigator-assigned anti-CMV Treatment, MBV=maribavir.
Percentages are based on the number of subjects in the Randomized Set.

[a] Confirmed CMV DNA level < LLOQ at the end of Week 8 (2 consecutive samples separated by at least 5 days with DNA levels < LLOQ [i.e.:, <137 IU/mL]).
[b] CMV DNA breakthrough=achieved confirmed CMV DNA level < LLOQ and subsequently became detectable.
c Other reasons=other reasons not including adverse events, deaths and lack of efficacy, withdrawal of consent, and non-compliance.
[d] Includes subjects who completed study assigned treatment and were non-responders.

The treatment effect was consistent across key subgroups and supports the generalizability of the study outcomes (see Table 6).

Table 6: Percentage of Responders by Subgroup in Study 303

	IAT (N=117)		LIVTENCITY 400 mg Twice Daily (N=235)	
	n/N	**%**	**n/N**	**%**
Transplant type				
SOT	18/69	26	79/142	56
HSCT	10/48	21	52/93	56
Baseline CMV DNA viral load				
Low	21/85	25	95/153	62
Intermediate/High	7/32	22	36/82	44
Genotypic resistance to other anti-CMV agents				
Yes	14/69	20	76/121	63
No	11/34	32	42/96	44
CMV syndrome/disease at baseline				
Yes	1/8	13	10/21	48
No	27/109	25	121/214	57
Age Group				
18 to 44 years	8/32	25	28/55	51
45 to 64 years	19/69	28	71/126	56
≥ 65 years	1/16	6	32/54	59

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=hematopoietic stem cell transplant, SOT=solid organ transplant

Recurrence

Recurrence requiring anti-CMV treatment after Week 8 was reported for 34/131 (26.0%) LIVTENCITY patients compared to 10/28 (35.7%) IAT patients. The median time to recurrence after CMV viremia clearance was 21 days (range 13, 80) in the LIVTENCITY group and 22 days (range 14, 36) in the IAT group.

Rescue Arm

Twenty-two patients received LIVTENCITY as rescue therapy due to worsening of CMV viremia or new/persistent symptomatic CMV infections 7 (31.8%) or lack of improvement in CMV infection plus intolerance to IAT 15 (68.2%). Of the 22 patients, 11 (50.0%) patients achieved confirmed CMV viremia clearance at Week 8 of the LIVTENCITY rescue treatment phase and 11 (50.0%) patients were nonresponders.

Phase 2 Studies

Study 202 (NCT01611974) was a Phase 2, randomized study to assess the safety and anti-CMV activity of 400 mg, 800 mg, and 1200 mg twice daily of LIVTENCITY for the treatment of 120 transplant recipients with CMV infections that are resistant or refractory to treatment with ganciclovir/valganciclovir or foscarnet. By Week 6, 28/40 (70%) patients receiving 400 mg twice daily had achieved confirmed undetectable plasma CMV DNA. The mean (SD) exposure to patients receiving 400 mg LIVTENCITY-treated patients was 85 (55) days with a maximum of 177 days. The virologic response of doses of 400 mg, 800 mg or 1200 mg twice daily of LIVTENCITY were comparable within 6 weeks.

Study 203 was a Phase 2, randomized, dose-ranging study to assess the safety and anti-CMV activity of 400 mg, 800 mg and 1200 mg twice daily LIVTENCITY versus valganciclovir for the pre-emptive treatment of 159 SOT or HSCT recipients with CMV infection without CMV organ disease or resistant/refractory CMV infection. By Weeks 3 and 6, 26/40 (65%) and 31/40 (78%) patients receiving 400 mg twice daily had achieved confirmed undetectable plasma CMV DNA compared to 22/40 (55%) and 26/40 (65%) patients receiving valganciclovir, respectively. The mean (SD) exposure to patients receiving 400 mg of LIVTENCITY was 50 (29) days with a maximum of 92 days. The virologic response of doses up to 1200 mg twice daily and durations of up to 12 weeks of LIVTENCITY were comparable. Overall, the favorable results observed in Study 303 were consistent with the results from the Phase 2 studies; thus, these earlier studies provide further support for the use of LIVTENCITY in the treatment of post-transplant CMV infection and disease in adults.

5.2 Pharmacokinetic Properties

Maribavir pharmacological activity is due to the parent drug. The pharmacokinetics of maribavir have been characterised following oral administration in healthy subjects and transplant patients. Maribavir exposure increased in approximately dose proportionally. In healthy subjects, the geometric mean steady-state $AUC_{0-\tau}$, $C_{max,}$ and C_{trough} values were 101µg*h/mL, 16.4 µg/mL, and 2.89 µg/mL, respectively, following 400 mg twice daily oral maribavir doses. In transplant recipients, maribavir steady state exposure following oral administration of 400 mg twice daily doses are provided below, based on a population pharmacokinetics analysis. Steady-state was reached in 2 days, with an accumulation ratio of 1.47 for AUC and 1.37 for C_{max}.

Table 7: Maribavir Pharmacokinetic Properties Based on a Population Pharmacokinetics Analysis

Parameter GM (% CV)	$AUC_{0-\tau}$ µg*h/mL	C_{max} µg/mL	C_{trough} µg/mL
Maribavir 400 mg twice daily	142 (48.5%)	20.1 (35.5%)	5.43 (85.9%)

GM: Geometric mean, % CV: Geometric coefficient of variation

Absorption

Maribavir was rapidly absorbed with peak plasma concentrations occuring 1.0 to 3.0 hours post dose. Exposure to maribavir is unaffected by crushing the tablet, administration of crushed tablet through nasogastric (NG)/orogastric tubes, or coadministation with proton pump inhibitors (PPIs), histamine H2 receptor antagonists (H2 blockers), or antacids.

The intrasubject variability (< 22%) and intersubject variability (< 37%) in maribavir PK parameters are low to moderate.

Effect of Food

In healthy subjects, oral administration of a single 400 mg dose of maribavir with a high fat, high caloric meal did not have any statistically significant effect on the overall exposure (AUC) and resulted in 28% decrease in C_{max} of maribavir. Maribavir can be administered orally with or without food as has been done in the clinical studies.

Distribution

Based on population pharmacokinetic analyses, the mean apparent steady-state volume of distribution is estimated to be 24.9 L.

In vitro binding of maribavir to human plasma proteins was 98.0% over the concentration range of 0.05-200 µg/mL. *Ex vivo* protein binding of maribavir (98.5%-99.0%) was consistent with *in vitro* data, with no apparent difference observed among healthy subjects, subjects with hepatic (moderate) or renal (mild, moderate or severe) impairment, human immunodeficiency virus (HIV) patients, or transplant patients.

Maribavircan penetrate the blood-retinal barrier and may cross the blood-brain barrier but CNS penetration is expected to be low compared to plasma levels *(see Special Warnings and Special Precautions for Use, 4.4 and Nonclinical Safety Data, 5.3)*.

In vitro data indicate that maribavir is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and organic cation transporter 1(OCT1) transporters. Changes in maribavir plasma concentrations due to inhibition of P-gp/BCRP/OCT1 were not clinically relevant.

Metabolism

Maribavir is primarily eliminated by hepatic metabolism via CYP3A4 (primary metabolic pathway fraction metabolised estimated to be at least 35%), with secondary contribution from CYP1A2 (fraction metabolised estimated at no more than 25%). The major metabolite of maribavir is formed by N-dealkylation of the isopropyl moiety and is considered pharmacologically inactive. The metabolic ratio for this major metabolite in plasma was 0.15-0.20. Multiple UGT enzymes, namely UGT1A1, UGT1A3, UGT2B7, and possibly UGT1A9, are involved in the glucuronidation of maribavir in humans, however, the contribution of glucuronidation to the overall clearance of maribavir is low based on *in vitro* data.
In vitro studies, metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, UGT1A4, UGT1A6, UGT1A10, or UGT2B15.

Excretion and Elimination

The mean terminal elimination half-life and oral clearance of maribavir are 4.32 hours and 2.67 L/h, respectively, in transplant patients. After single-dose oral administration of [^{14}C]-maribavir, approximately 61% and 14% of the radioactivity were recovered in urine and feces, respectively, primarily as the major and inactive metabolite. Urinary excretion of unchanged maribavir is minimal.

Special Populations

Impaired Renal Function

No clinically significant effect of mild/moderate (CLcr, between 30 and 80 mL/min) or severe (CLcr less than 30 mL/min) renal impairment was observed on maribavir total PK parameters following a single dose of 400 mg maribavir. The difference in maribavir PK parameters between subjects with mild/moderate or severe renal impairment and subjects with normal renal function was less than 9%.

Impaired Hepatic Function

No clinically significant effect of moderate hepatic impairment (Child-Pugh Class B, score of 7-9) was observed on total or unbound maribavir PK parameters following a single dose of 200 mg of maribavir. Compared to the healthy control subjects, AUC and C_{max} were 26% and 35% higher, respectively, in subjects with moderate hepatic impairment.

Age, Gender, Race. Weight and Transplant Type

Age (18-79 years), gender, race (Caucasian, Black, Asian, or others), ethnicity (Hispanic/Latino or non-Hispanic/Latino), body weight (36 to 141 kg) and transplant type did not have clinically

significant effect on the pharmacokinetics of maribavir based on population PK analysis.

Transplant Types

Transplant types (HSCT vs. SOT) or between SOT types (liver, lung, kidney, or heart) or presence of gastrointestinal (GI) graft-versus host disease (GvHD) do not have a clinically significant impact on PK of maribavir.

5.3 Nonclinical Safety Data

Carcinogenesis, Mutagenesis, Reproductive Toxicology

Two-year carcinogenic studies were conducted in both mice and rats at doses up to 150 and 100 mg/kg/day, respectively. No carcinogenic potential was identified in rats up to 100 mg/kg/day, at which exposures in males and females were 0.2 and 0.36 times, respectively the human exposure at the RHD. In male mice, an equivocal elevation in the incidence of hemangioma, hemangiosarcoma, and combined hemangioma/ hemangiosarcoma across multiple tissues at 150 mg/kg/day is of uncertain relevance in terms of its translation to human risk given the lack of an effect in female mice or in rats after 104 weeks of administration, no neoplastic proliferative effects in male and female mice after 13 weeks administration, the negative genotoxicity package, and the difference in duration of administration in humans. There were no carcinogenic findings at the next lower dose of 75 mg/kg/day, which is approximately 0.35 and 0.25 in males and females, respectively, the human exposure at the RHD. LIVTENCITY was not mutagenic in a bacterial mutation assay. In the mouse lymphoma assay, LIVTENCITY demonstrated mutagenic potential in the absence of metabolic activation and the results were equivocal in the presence of metabolic activation (not concentration-dependent and not reproduced in the repeat assay). LIVTENCITY was not clastogenic in the in vivo rat bone marrow micronucleus assay up to very high dose of 1200 mg/kg that was toxic and close to producing lethality. Given the negative results of the in vivo rat micronucleus assay the weight of evidence indicates that LIVTENCITY does not exhibit genotoxic potential.
LIVTENCITY did not affect embryofetal growth or development, nor produce any malformations, and was not teratogenic in pregnant rats or rabbits, at doses up to 400 mg/kg/day and 100 mg/kg/day, respectively (1.1 and 0.45 times higher than human exposure at the RHD, respectively). However, in rats, decreases in sperm straight-line velocity, without an effect on fertility were noted in males at doses ≥100 mg/kg/day (which is estimated to be less than the human exposure at the RHD). Decreases in the number of viable fetuses and increases in early resorptions and post-implantation losses were observed in females only at maternally toxic doses

≥100 mg/kg/day (which is approximately 0.5 times the human exposure at the RHD).
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 LIVTENCITY. No effects were observed at 50 mg/kg/day, which is estimated to be less than the human exposure at the RHD).

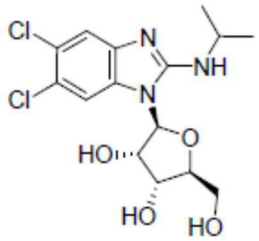
Animal Toxicology and/or Pharmacology

In repeat-dose oral toxicity studies in rats (26 weeks) and monkeys (52 weeks), the major findings were regenerative anemia and histologic change of mucosal cell hyperplasia in the intestinal tract at doses ≥25 mg/kg/day in rats and at doses ≥100 mg/kg/day in monkeys, which was associated with dehydration in both species, and clinical observations of soft to liquid stool, and electrolyte changes (in monkeys only). The anemia and intestinal hyperplasia were reversible or showed progression to recovery after cessation of dosing. A no observed adverse effect level (NOAEL) was not established in monkeys and was therefore considered to be <100 mg/kg/day, which is approximately 0.25 the human exposure at the RHD. In rats the NOAEL was 25 mg/kg/day, at which exposures were 0.05 and 0.1 times the human exposure at the RHD in males and females, respectively.
LIVTENCITY did not demonstrate phototoxicity in vitro, therefore, the potential for phototoxicity in humans is considered unlikely.
Whole body autoradiography data demonstrate LIVTENCITY is not expected to cross the blood brain barrier in humans to a significant extent.

6. Pharmaceutical Particulars

Chemical Structure

The chemical name of LIVTENCITY is 5,6-Dichloro-2-(isopropylamino)-1-β-L-ribofuranosyl-1*H*-benzimidazole and the structural formula is:



The molecular formula for LIVTENCITY is $C_{15}H_{19}Cl_2N_3O_4$ and its molecular weight is 376.24.

6.1 List of Excipients

Tablet Core

Microcrystalline cellulose

Sodium starch glycolate

Magnesium stearate

Film Coating

Polyvinyl alcohol

Macrogol (i.e., polyethylene glycol)

Titanium dioxide

Talc

Brilliant blue FCF aluminium lake (FD&C Blue #1)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Refer to product packaging.

6.4 Special Precautions for Storage

Do not store above 30°C.

Store tablets in the original packaging.

6.5 Nature and Contents of Container

Maribavir 200 mg tablets are provided in a 60cc high-density polyethylene (HDPE) white square bottle with induction sealed and a child resistant cap. Each container contains 28 count or 56 count tablets.

Not all pack sizes may be available locally.

6.6 Instructions for Use/Handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 Product Registrant

TAKEDA PHARMACEUTICALS (ASIA PACIFIC) PTE. LTD.
8, MARINA BOULEVARD, #05-02,
MARINA BAY FINANCIAL CENTRE,
SINGAPORE 018981

8 Date of Revision

Mar 2025
Reference: CCDSv3.0