SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

LIVTENCITY 200 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 mg maribavir.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Blue, oval shaped convex tablet of 15.5 mm, debossed with “SHP” on one side and “620” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

LIVTENCITY is indicated for the treatment of cytomegalovirus (CMV) infection and/or disease that are 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.

4.2 Posology and method of administration

LIVTENCITY should be initiated by a physician experienced in the management of patients who have undergone solid organ transplant or haematopoietic stem cell transplant.

Posology

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.

Co-administration with CYP3A inducers

Co-administration of LIVTENCITY with the strong cytochrome P450 3A (CYP3A) inducers rifampicin, rifabutin or St. John's wort is not recommended due to potential for a decrease in efficacy of maribavir.

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 1 200 mg twice daily (see sections 4.4, 4.5 and 5.2).

Missed dose

Patients should be instructed that if they miss a dose of LIVTENCITY, and the next dose is due within the next 3 hours, they should skip the missed dose and continue with the regular schedule. Patients should not double their next dose or take more than the prescribed dose.

Special populations

Elderly patients

No dose adjustment is required for patients over 65 years (see sections 5.1 and 5.2).

Renal impairment

No dose adjustment of LIVTENCITY is required 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. No dose adjustments is expected to be required for patients on dialysis due to the high plasma protein binding of maribavir (see section 5.2).

Hepatic impairment

No dose adjustment of LIVTENCITY is required 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**.** It is not known whether exposure to maribavir will significantly increase in patients with severe hepatic impairment. Therefore, caution is advised when LIVTENCITY is administered to patients with severe hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of LIVTENCITY in patients below 18 years of age have not been established. No data are available.

Method of administration

Oral use.

LIVTENCITY is intended for oral use only and can be taken with or without food. The film-coated tablet can be taken as a whole tablet, a crushed tablet, or a crushed tablet through a nasogastric or orogastric tube.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Co-administration with ganciclovir or valganciclovir (see section 4.5).

4.4 Special warnings and precautions for use

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. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. CMV DNA levels should be monitored and resistance mutations should be investigated in patients who do not respond to treatment. Treatment should be discontinued if maribavir resistance mutations are detected.

CMV disease with CNS involvement

LIVTENCITY was not studied in patients with CMV CNS infection. Based on nonclinical data, CNS penetration of maribavir is expected to be low compared to plasma levels (section 5.2 and 5.3). Therefore, LIVTENCITY is not expected to be effective in treating CMV CNS infections (e.g. meningo-encephalitis).

Use with immunosuppressants

LIVTENCITY has the potential to increase the concentrations of immunosuppressants that are cytochrome P450 (CYP)3A/P-gp substrates with narrow therapeutic margins (including tacrolimus, cyclosporine, sirolimus and everolimus). The plasma levels of these immunosuppressants must be frequently monitored throughout treatment with LIVTENCITY, especially following initiation and after discontinuation of LIVTENCITY, and doses should be adjusted, as needed (see sections 4.5, 4.8 and 5.2).

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 sections 4.3 and 4.5).

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on maribavir

Maribavir is primarily metabolised by CYP3A, and medicinal products that induce or inhibit CYP3A are expected to affect the clearance of maribavir (see section 5.2).

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

Concomitant administration of strong or moderate CYP3A inducers, (such as rifampicin, rifabutin, carbamazepine, phenobarbital, phenytoin, efavirenz and St John's wort), is expected to significantly decrease maribavir plasma concentrations, which may result in decrease in efficacy. Therefore, alternative medicinal products with no CYP3A induction potential should be considered. Co-administration of maribavir with strong cytochrome P450 3A (CYP3A) inducers rifampicin, rifabutin or St. John's wort is not recommended.

If co-administration of maribavir with other strong or moderate CYP3A inducers (e.g., carbamazepine, efavirenz, phenobarbital and phenytoin) cannot be avoided, the maribavir dose should be increased
to 1 200 mg twice daily (see sections 4.2 and 5.2).

Effect of maribavir on other medicinal products

Co-administration of maribavir with valganciclovir and ganciclovir is contraindicated (see section 4.3). LIVTENCITY may antagonise 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 sections 4.3 and 5.1).

At therapeutic concentrations, clinically relevant interactions are not expected when maribavir is co-administered with substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2E1, 2D6, and 3A4; UGT1A1, 1A4, 1A6, 1A9, 2B7; bile salt export pump (BSEP); multidrug and toxin extrusion protein (MATE)/2K; organic anion transporters (OAT)1; organic cation transporters (OCT)1 and OCT2; organic anion transporting polypeptide (OATP)1B1 and OATP1B3 based on *in vitro* and clinical interaction results (Table 1 and section 5.2).

Maribavir acted as an inducer of CYP1A2 enzyme in vitro. There are no clinical data available to exclude an interaction risk via CYP1A2 induction in vivo. Therefore, the concomitant administration of maribavir and medicinal products that are sensitive substrates of CYP1A2 with a narrow therapeutic window (e.g., tizanidine and theophylline) should be avoided due to the risk for lack of efficacy of CYP1A2 substrates.

Co-administration of maribavir increased plasma concentrations of tacrolimus (see Table 1). When the immunosuppressants tacrolimus, cyclosporine, everolimus or sirolimus are co-administered with maribavir, immunosuppressant levels should be frequently monitored throughout treatment with maribavir, especially following initiation and after discontinuation of maribavir and dose adjusted, when needed (see sections 4.4 and Table 1).

Maribavir inhibited P-gp transporter *in vitro* at clinically relevant concentrations. In a clinical study, co-administration of maribavir increased plasma concentrations of digoxin (see Table 1 Therefore, caution should be exercised when maribavir and sensitive P-gp substrates (e.g., digoxin, dabigatran) are co-administered. Serum digoxin concentrations should be monitored, and dose of digoxin may need to be reduced, as needed (see Table 1).

Maribavir inhibited BCRP transporter *in vitro* at clinically relevant concentrations. Therefore, co-administration of maribavir with sensitive BCRP substrates such as rosuvastatin, is expected to increase their exposure and lead to undesirable effects.

In vitro, maribavir inhibits OAT3, therefore, plasma concentrations of medicinal products transported by OAT3 may be increased (e.g.: ciprofloxacin, imipenem, and cilastatin).

In vitro, maribavir inhibits MATE1. There are no clinical data available whether the co-administration of maribavir with sensitive MATE1 substrates (e.g., metformin) could potentially lead to clinically relevant interactions.

General information

If dose adjustments of concomitant medicinal products are made due to treatment with maribavir, doses should be readjusted after treatment with maribavir 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 maribavir or are predicted medicinal product interactions that may occur with maribavir (see sections 4.4 and 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 co-administration 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.
pantoprazole	Interaction not studied. Expected: ↔ maribavir	No dose adjustment is required.
omeprazole	↔ maribavir ↑ plasma omeprazole/5-hydroxyomeprazole concentration ratio 1.71 (1.51, 1.92) at 2h post-	No dose adjustment is required.

Medicinal product by therapeutic area	**Effect on geometric mean ratio (90 % CI) (likely mechanism of action)**	**Recommendation concerning co-administration with maribavir**
	dose (CYP2C19 inhibition)	
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 co-administered. Monitor serum digoxin concentrations. The dose of sensitive P-gp substrates such as digoxin may need to be reduced when co-administered with maribavir.
Antibiotics		
clarithromycin	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Anticonvulsants		
carbamazepine phenobarbital phenytoin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to 1 200 mg twice daily is recommended when co-administration with these anticonvulsants.
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 and P-gp inhibition)	No dose adjustment is required.
voriconazole (200 mg twice daily, maribavir 400 mg twice daily)	Expected: ↑ maribavir (CYP3A inhibition) ↔ voriconazole AUC 0.93 (0.83, 1.05) C_{max} 1.00 (0.87, 1.15) (CYP2C19 inhibition)	No dose adjustment is required.
Antihypertensives		
diltiazem	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Antimycobacterials		
rifabutin	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	Co-administration of maribavir and rifabutin is not recommended due to potential for a decrease in efficacy of maribavir.

Medicinal product by therapeutic area	**Effect on geometric mean ratio (90 % CI) (likely mechanism of action)**	**Recommendation concerning co-administration with maribavir**
rifampicin (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)	Co-administration 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)	Co-administration of maribavir and St. John's wort is not recommended due to potential for a decrease in efficacy of maribavir.
HIV antiviral agents		
Non-nucleoside reverse transcriptase inhibitors		
Efavirenz Etravirine Nevirapine	Interaction not studied. Expected: ↓ maribavir (CYP3A induction)	A dose adjustment of maribavir to 1 200 mg twice daily is recommended when co-administration with these a non-nucleoside reverse transcriptase inhibitors.
Nucleoside reverse transcriptase inhibitors		
Tenofovir disoproxil Tenofovir alafenamide Abacavir Lamivudine Emtricitabine	Interaction not studied. Expected: ↔ maribavir ↔ nucleoside reverse transcriptase inhibitors	No dose adjustment is required.
Protease inhibitors		
ritonavir- boosted protease inhibitors (atazanavir, darunavir, lopinavir)	Interaction not studied. Expected: ↑ maribavir (CYP3A inhibition)	No dose adjustment is required.
Integrase strand transfer inhibitors		
dolutegravir	Interaction not studied. Expected: ↔ maribavir ↔ dolutegravir	No dose adjustment is required.
HMG-CoA reductase inhibitors		
atorvastatin fluvastatin simvastatin	Interaction not studied. Expected: ↑ HMG-CoA reductase inhibitors (BCRP inhibition)	No dose adjustment is required.

Medicinal product by therapeutic area	Effect on geometric mean ratio (90 % CI) (likely mechanism of action)	Recommendation concerning co-administration with maribavir
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 maribavir 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 maribavir 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 dose, maribavir 400 mg twice daily for 7 days)	↔ 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
*$AUC_{0-\infty}$ for single dose, AUC_{0-12} 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.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data of maribavir use in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). LIVTENCITY is not recommended during pregnancy and in women of childbearing potential not using contraception.

Maribavir is not expected to affect the plasma concentrations of systemically acting oral contraceptive steroids (see Section 4.5).

Breast-feeding

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 embryofoetal development study, however, a decrease in sperm straight line velocity was observed at doses ≥ 100 mg/kg/day (which is estimated to be < 1 times the human exposure at the recommended human dose [RHD]). There were no effects on reproductive organs in either males or females in nonclinical studies in rats and monkeys (see section 5.3).

4.7 Effects on ability to drive and use machines

LIVTENCITY has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Adverse events were collected during the treatment phase and follow-up phase through Study Week 20 in the Phase 3 study (see section 5.1). The mean exposures (SD) for LIVTENCITY was 48.6 (13.82) days with 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 (all occurring at < 1%).

Tabulated list of adverse reactions

The adverse reactions are listed below by body system organ class and frequency. Frequencies are defined as follows: 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) or very rare (< 1/10 000).

Table 2: Adverse reactions identified with LIVTENCITY

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

Description of selected adverse reactions*

Taste disturbance

Taste disturbance (comprised of 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, for most patients, resolved while patients remained on therapy (37%) or within a median of 7 days (Kaplan-Meier estimate, 95% CI: 4-8 days) after treatment discontinuation.

Increases in plasma levels of immunosuppressants

Immunosuppressant drug level increase (comprised of the preferred terms immunosuppressant drug level increased and drug level increased) occurred in 9% of patients treated with LIVTENCITY. LIVTENCITY has the potential to increase the drug concentrations of immunosuppressants that are CYP3A and/or P-gp substrates with narrow therapeutic ranges (including tacrolimus, cyclosporine, sirolimus and everolimus). (See sections 4.4, 4.5 and 5.2).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In Study 303, an accidental overdose of a single extra dose occurred in 1 LIVTENCITY-treated subject on Day 13 (1 200 mg total daily dose). No adverse reactions were reported.

In Study 202, 40 subjects were exposed to doses of 800 mg twice daily and 40 subjects were exposed to

1 200 mg twice daily for a mean of approximately 90 days. In Study 203, 40 subjects were exposed to doses of 800 mg twice daily and 39 subjects were exposed to 1 200 mg twice daily for a maximum of 177 days. There were no appreciable differences in the safety profile in either study compared to the 400 mg twice daily group in Study 303 in which subjects received maribavir for a maximum of 60 days.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AX10.

Mechanism of action

Maribavir is a competitive inhibitor of the UL97 protein kinase. UL97 inhibition occurs at the viral DNA replication phase, inhibiting UL97 serine/threonine kinase by competitively inhibiting the binding of ATP to the kinase ATP-binding site, without affecting the concatemer maturation process, abolishing phosphotransferase inhibiting CMV DNA replication and maturation, CMV DNA encapsidation, and CMV DNA nuclear egress.

Antiviral activity

Maribavir inhibited human CMV replication in virus yield reduction, DNA hybridization, and plaque reduction assays in human lung fibroblast cell line (MRC-5), human embryonic kidney (HEK), and human foreskin fibroblast (MRHF) cells. 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. No significant difference in EC_{50} values across the four human CMV glycoprotein B genotypes (N = 2, 1, 4, and 1 for gB1, gB2, gB3, and gB4, respectively) was seen.

Combination antiviral activity

When maribavir was tested in *in vitro* combination with other antiviral compounds, strong antagonism was seen with ganciclovir.

No antagonism was seen in combination with cidofovir, foscarnet and letermovir.

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, V356G, L397R, T409M, H411L/N/Y, D456N, V466G, C480F, P521L, and Y617del. 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 301311del) conferred only mild maribavir resistance (< 5-fold increase in EC_{50}), while L335P conferred high maribavir resistance.

In clinical studies

In Phase 2 Study 202 and Study 203 evaluating maribavir in 279 HSCT or SOT recipients, post-treatment pUL97 genotyping data from 23 of 29 patients who initially achieved viraemia 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, whereas the pUL27 mutation G344D showed no difference in maribavir EC_{50} as compared to the wild-type strain.

In Phase 3 Study 303 evaluating maribavir in patients with phenotypic resistance to valganciclovir/ganciclovir, DNA sequence analysis of the entire coding regions of pUL97 and pUL27 was performed on 134 paired sequences from maribavir-treated patients. The treatment-emergent pUL97 substitutions F342Y (4.5-fold), T409M (78-fold), H411L/N/Y (69-, 9-, and 12-fold, respectively), and/or C480F (224-fold) were detected in 60 subjects and were associated with non-response (47 subjects were on-treatment failures and 13 subjects were relapsers). One subject with the pUL27 L193F substitution (2.6-fold reduced susceptibility to maribavir) at baseline did not meet the primary endpoint. In addition, the following multiple mutations were associated with non-response; F342Y+T409M+H411N (78-fold), C480F+H411L+H411Y (224-fold), F342Y+H411Y (56-fold), T409M+C480F (224-fold), H411Y+C480F (224-fold), H411N+C480F (224-fold), and T409M+H411Y (78-fold).

Cross resistance

Cross-resistance has been observed between maribavir and ganciclovir/valganciclovir (vGCV/GCV) in cell culture and in clinical studies. In the Phase 3 Study 303, a total of 46 patients in the maribavir arm had a treatment emergent resistance associated substitutions (RAS) to Investigator assigned treatment (IAT). Of these 24 had treatment-emergent C480F or the F342Y RAS, both are cross-resistant to both ganciclovir/valganciclovir and maribavir. Of these 24 patients, 1 (4%) achieved the primary endpoint. Overall, only nine of these 46 patients achieved the primary endpoint.
pUL97 vGCV/GCV resistance-associated substitutions F342S/Y, K355del, V356G, D456N, V466G, C480R, P521L, and Y617del reduce susceptibility to maribavir > 4.5-fold. Other vGCV/GCV resistance pathways have not been evaluated for cross-resistance to maribavir. pUL54 DNA polymerase substitutions conferring resistance to vGCV/GCV, cidofovir, or foscarnet remained susceptible to maribavir.

Substitutions pUL97 F342Y and C480F are maribavir treatment-emergent resistance-associated substitutions that confer > 1.5-fold reduced susceptibility to vGCV/GCV, a fold reduction that is associated with phenotypic resistance to vGCV/GCV. The clinical significance of this cross-resistance to vGCV/GCV for these substitutions has not been determined. Maribavir resistant virus remained susceptible to cidofovir and foscarnet. Additionally, there are no reports of any pUL27 maribavir resistance-associated substitutions being evaluated for vGCV/GCV, cidofovir, or foscarnet cross-resistance. Given the lack of resistance-associated substitutions for these drugs mapping to pUL27, cross-resistance is not expected for pUL27 maribavir substitutions.

Clinical efficacy

A Phase 3, multi-centre, randomised, open-label, active-controlled superiority study (Study SHP620-303) assessed the efficacy and safety of LIVTENCITY treatment compared to Investigator assigned treatment (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. Refractory CMV infection was defined as documented failure to achieve > 1 log10 decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with intravenous

ganciclovir/oral valganciclovir, intravenous foscarnet, or intravenous cidofovir. This definition was applied to the current CMV infection and the most recently administered anti-CMV agent.

Patients were stratified by transplant type (HSCT or SOT) and screening CMV DNA levels and then randomised in a 2:1 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.

The mean age of trial subjects was 53 years and most subjects were male (61%), white (76%) and not Hispanic or Latino (83%), with similar distributions across the two treatment arms. Baseline disease characteristics are summarised in Table 3 below.

Table 3: Summary of the baseline disease characteristics of the study population in Study 303

Characteristic[a]	**IAT (N=117)**	**LIVTENCITY 400 mg Twice Daily (N=235)**
IAT treatment prior to randomisation, n (%)[b]		
Ganciclovir/ Valganciclovir	98 (84)	204 (87)
Foscarnet	18 (15)	27 (12)
Cidofovir	1 (1)	4 (2)
IAT treatment after randomisation, n (%)		
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[d]	32 (46)	74 (52)
Lung[d]	22 (32)	40 (28)
Heart[d]	9 (13)	14 (10)
Multiple[d]	5 (7)	5 (4)
Liver[d]	1 (1)	6 (4)
Pancreas[d]	0	2 (1)
Intestine[d]	0	1 (1)
CMV DNA levels category as reported by central laboratory, n (%)[e]		
High	7 (6)	14 (6)
Intermediate	25 (21)	68 (29)
Low	85 (73)	153 (65)
Baseline symptomatic CMV infection[f]		
No	109 (93)	214 (91)
Yes[f]	8 (7)	21 (9)
CMV syndrome (SOT only), n (%)[d, f, g]	7 (88)	10 (48)
Tissue invasive disease, n (%)[f, d, g]	1 (13)	12 (57)

CMV=cytomegalovirus, DNA=deoxyribonucleic acid, HSCT=haematopoietic stem cell transplant, IAT=investigator assigned anti-CMV treatment, max=maximum, min=minimum, N=number of patients, 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 randomisation for patients who did not receive study-assigned treatment.
[b] Percentages are based on the number of subjects in the randomised set within each column. Most recent anti-CMV agent, used to confirm refractory eligibility criteria.
[c] The most recent transplant.
[d] Percentages are based on the number of patients within the category.
[e] 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).
[f] Confirmed by Endpoint Adjudication Committee (EAC).
[g] Patients could have CMV syndrome and tissue invasive disease.

The primary efficacy endpoint was confirmed CMV viraemia clearance (plasma CMV DNA concentration below the lower limit of quantification (< LLOQ; i.e. < 137 IU/mL) at Week 8 regardless of whether either study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy. The key secondary endpoint was CMV viraemia clearance and CMV infection symptom control at Week 8 with maintenance of this treatment effect through Study Week 16. 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.

For the primary endpoint, LIVTENCITY was superior to IAT (56% vs. 24%, respectively, $p < 0.001$). For the key secondary endpoint, 19% vs. 10% achieved both CMV viraemia clearance and CMV infection symptom control in the LIVTENCITY and IAT group, respectively (p=0.013) (see Table 4).

Table 4: Primary and key secondary efficacy endpoint analysis (randomised set) in Study 303

	IAT (N=117) n (%)	**LIVTENCITY 400 mg twice daily (N=235) n (%)**
Primary endpoint: CMV viraemia 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 viraemia 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=haematopoietic 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.
[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 treatment effect was consistent across transplant type, age group, and the presence of CMV syndrome/disease at baseline. However, LIVTENCITY was less effective against subjects with increased CMV DNA levels (≥ 50 000 IU/mL) and patients with absence of genotypic resistance (see Table 5).

Table 5: 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	15/70	21	76/121	63
No	10/33	30	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=haematopoietic stem cell transplant, SOT=solid organ transplant

Recurrence

The secondary endpoint of recurrence of CMV viraemia was reported in 57% of the maribavir treated patients and in 34% of the IAT treated patients. Of these, 18% in the maribavir group had recurrence of CMV viraemia while on-treatment compared to 12% the IAT group. Recurrence of CMV viraemia during follow up was seen in 39% of patients in the maribavir group and in 22% of the patients in the IAT group.

Overall mortality: All-cause mortality was assessed for the entire study period. A similar percentage of subjects in each treatment group died during the trial (LIVTENCITY 11% [27/235]; IAT 11% [13/117]).

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with LIVTENCITY in one or more subsets of the paediatric population for treatment of cytomegalovirus infection (see section 4.2).

5.2 Pharmacokinetic properties

Maribavir pharmacological activity is due to the parent medicinal product. The pharmacokinetics of maribavir have been characterised following oral administration in healthy subjects and transplant patients. Maribavir exposure increased in an approximately dose proportionally manner. In healthy subjects, the geometric mean steady-state AUC_{0-t}, C_{max} and C_{trough} values were 101 µg*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}. The intrasubject variability (< 22%) and intersubject variability (< 37%) in maribavir PK parameters are low to moderate.

Table 6: Maribavir pharmacokinetic properties in transplant recipients based on a population pharmacokinetics analysis

Parameter GM (% CV)	**$AUC_{0-\underline{tau}}$ 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 occurring 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 co-administration with proton pump inhibitors (PPIs), histamine H_2 receptor antagonists (H_2 blockers) or antacids.

Effect of food

In healthy subjects, oral administration of a single 400 mg dose of maribavir with a high fat, high caloric meal resulted in no change in the overall exposure (AUC) and a 28% decrease in C_{max} of maribavir, which was not considered clinically relevant.

Distribution

Based on population pharmacokinetic analyses, the 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.

Maribavir may cross the blood-brain barrier in humans but CNS penetration is expected to be low compared to plasma levels (see section 4.4 and 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.

Biotransformation

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.

Based on *in vitro* studies, metabolism of maribavir is not mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP3A5, 1A4, UGT1A6, UGT1A10, or UGT2B15.

Elimination

The elimination half-life and oral clearance of maribavir are estimated at 4.3 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 faeces, respectively, primarily as the major and inactive metabolite. Urinary excretion of unchanged maribavir is minimal.

Special populations

Renal impairment

No clinically significant effect of mild, moderate or severe renal impairment (measured creatinine clearance ranging from 12 to 70 mL/min) 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 < 9%. As maribavir is highly bound to plasma proteins, it is unlikely that maribavir will be significantly removed by haemodialysis or peritoneal dialysis.

Hepatic impairment

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. It is not known whether the exposure to maribavir will increase in patients with severe hepatic impairment.

Age, gender, race, ethnicity, and weight

Age (18-79 years), gender, race (Caucasian, Black, Asian, or others), ethnicity (Hispanic/Latino or non-Hispanic/Latino) and body weight (36 to 141 kg) 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 Preclinical safety data

General

Regenerative anaemia and mucosal cell hyperplasia in the intestinal tract, observed with dehydration was noted in rats and monkeys, together with clinical observations of soft to liquid stool, and electrolyte changes (in monkeys only). A no observed adverse effect level (NOAEL) was not established in monkeys and was < 100 mg/kg/day, which is approximately 0.25 the human exposure at the recommended human dose (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.

Maribavir did not demonstrate phototoxicity *in vitro*, therefore, the potential for phototoxicity in humans is considered unlikely.

Maribavir was detected at low levels in the choroid plexus of rats and the brain and CSF of the monkey (see section 4.4 and 5.2).

Carcinogenesis

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 haemangioma, haemangiosarcoma, and combined haemangioma/ haemangiosarcoma 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, lack of 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.

Mutagenesis

Maribavir was not mutagenic in a bacterial mutation assay, nor clastogenic in the bone marrow micronucleus assay. In mouse lymphoma assays, maribavir demonstrated mutagenic potential in the absence of metabolic activation and the results were equivocal in the presence of metabolic activation. Overall, the weight of evidence indicates that maribavir does not exhibit genotoxic potential.

Reproduction

Fertility

In the combined fertility and embryofoetal development study in rats, there were no effects of maribavir on fertility. However, in male rats decreases in sperm straight line velocity, were observed at doses ≥ 100 mg/kg/day (which is estimated to be less than the human exposure at the RHD), but without any impact on male fertility.

Prenatal and postnatal development

In a combined fertility and embryofoetal development study in rats, maribavir was not teratogenic and had no effect on embryofoetal growth or development at doses up to 400 mg/kg/day. A decrease in the number of viable foetuses due to increase in early resorptions and post-implantation losses was observed in females at all tested maribavir doses which were also maternally toxic. The lowest dose corresponded to approximately half the human exposure at the RHD. In the pre and postnatal developmental toxicity study conducted in rats, decreased pup survival due to poor maternal care and reduced body weight gain associated with a delay in developmental milestones (pinna detachment, eye opening and preputial separation) were observed at maribavir doses ≥ 150 mg/kg/day. Postnatal development was not affected at 50 mg/kg/day. Fertility and mating performance of the F_1 generation, and their ability to maintain pregnancy and to deliver live offspring, was unaffected up to 400 mg/kg/day.

In rabbits, maribavir was not teratogenic at doses up to 100 mg/kg/day (approximately 0.45 times the human exposure at the RHD).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460(i))

Sodium starch glycolate

Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)

Macrogol (polyethylene glycol) (E1521)

Titanium dioxide (E171)

Talc (E553b)

Brilliant blue FCF aluminum lake (EU) (E133)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with child resistant cap.

Pack-sizes of 28, 56 or 112 (2 bottles of 56) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

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