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Newcastle University

Health Technology Briefing
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Maribavir for treating cytomegalovirus infection after haematopoietic stem cell transplant

Company/Developer	Takeda UK Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33348	NICE ID: 10721	UKPS ID: 662178

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Maribavir is being developed as a first-line pre-emptive therapy for adults with cytomegalovirus (CMV) infection post haematopoietic stem cell transplant (HSCT). CMV is a common virus that usually only causes mild infection. In people with weakened immunity, such as transplant patients receiving treatment that reduce the activity of the immune system, CMV can cause serious infection. CMV disease can affect several organs in the body, such as the eyes, lungs, and the gastrointestinal tract (the stomach and intestines) and cause organ failure. CMV disease is chronically debilitating and life-threatening. Prevention and treatment of CMV infection after transplantation has been challenged by the limited number of available antivirals and toxicity associated with currently available drugs.

Maribavir, administered orally, is thought to block the action of a viral enzyme called UL97 kinase that is necessary for the virus for many processes. By blocking the enzyme, the medicine is expected to prevent viruses from reaching maturity, so that no new infectious viruses can be produced. If licenced, maribavir will provide an additional first-line pre-emptive antiviral therapy for adults with asymptomatic CMV infection post HSCT.

Proposed Indication

Treatment of cytomegalovirus (CMV) infection first-line pre-emptive therapy post haematopoietic stem cell transplant (HSCT).[1]

Technology

Description

Maribavir (TAK-620, SHP620) is a potent, selective, orally bioavailable benzimidazole riboside that is active against CMV infection in humans.[2] Maribavir is active *in vitro* against CMV strains that are resistant to current anti-CMV agents such as ganciclovir, foscarnet, or cidofovir. It has anti-CMV effects on CMV DNA synthesis, viral gene expression, encapsidation, and viral capsid egress through the inhibition of UL97-mediated phosphorylation of nuclear lamin A/C.[3] The UL97 kinase has important roles in the replication of CMV, such that genetic knockout or maribavir suppression of its function severely impairs viral growth but does not prevent it entirely.[4]

Maribavir is currently in clinical development for the treatment of CMV as the first episode of CMV viremia after HSCT. In the phase III clinical trial (NCT02927067), participants received maribavir 400mg twice daily via oral tablet for 8 weeks.[5]

Key Innovation

Currently available anti-CMV drugs are effective but limited by toxicities including myelosuppression.

Unlike available anti-CMV drugs that inhibit DNA polymerase, maribavir blocks nuclear egress of viral capsids through the inhibition of the UL97 kinase. Additionally, maribavir is active *in vitro* against CMV strains that are resistant to current standard of care treatments.[2] The unique mechanism of action means cross-resistance with current anti-CMV drugs, like (val)ganciclovir, foscarnet, and cidofovir, is not a concern.[6] Maribavir also has a favorable safety profile, without associated myelosuppression or nephrotoxicity.[2]

If licensed, maribavir may be of significant benefit in the prevention of CMV disease in adult allogenic HSCT recipients, mainly because it has a new mechanism of action and tolerable safety profile.[7]

Regulatory & Development Status

Maribavir does not currently have Marketing Authorisation in the EU/UK for any indication.

In November 2021, the U.S. Food and Drug Administration approved maribavir as the first drug for treating adults and pediatric patients (12 years of age and older and weighing at least 35 kilograms) with post-transplant cytomegalovirus (CMV) infection/disease that does not respond (with or without genetic mutations that cause resistance) to available antiviral treatment for CMV.[8]

Maribavir was awarded orphan drug designation by the European Medicines Agency (EMA) in 2013 for the treatment of CMV disease in patients with impaired cell-mediated immunity.[7]

In January 2018, maribavir was granted Breakthrough Therapy Designation by US Food and Drug Administration (FDA) for the treatment of CMV infection in transplant patients resistant or refractory to prior therapy.[9]

Patient Group

Disease Area and Clinical Need

CMV is a herpes virus and a common viral infection.[10,11] The various strains of CMV are species specific and produce a cytopathic effect resulting in greatly enlarged (cytomegalic) cells containing cytoplasmic and intranuclear inclusions.[12] Once a person is infected, CMV stays in the body for life and the person will have CMV antibodies (known as 'seropositive'). The virus is carried by around 50–80% of the population. For healthy people, CMV usually remains dormant and does not cause symptoms.[11] However, reactivation of CMV in immunocompromised individuals, such as those undergoing HSCT, is clinically severe and can cause severe and potentially lethal complications such as pneumonitis, colitis, retinitis and encephalitis.[13-15] The major risk factors are when the recipient is CMV seronegative and the donor is seropositive as well as when lymphocyte-depleting antibodies are used.[16]

In 2020, 1,476 patients received allogeneic HSCTs in the UK.[17] CMV reactivation rate has been reported in 30-70% HSCT patients which would equate to 442 to 1033 patients using 2020 figures. Mortality related to fatal CMV disease is still as high as 45–60% in HSCT recipients.[18] The 2020-2021 Hospital Episodes Statistics for England recorded a total of 384 finished consultant episodes (FCE) for CMV disease (ICD-10 code: B25.9 Cytomegaloviral disease, unspecified), resulting in 251 hospital admissions and 2,448 FCE bed days and 52 day cases.[19]

Recommended Treatment Options

According to the National Institute for Health and Care Excellence (NICE), letermovir is indicated for the prophylaxis of CMV reactivation or disease in people with seropositive-CMV who have had an allogeneic HSCT.[20]

Ganciclovir (GCV) and valganciclovir (VGCV) have a licence for use in the treatment and/or prevention of CMV infection and disease following transplant:

- GCV is indicated in adults and adolescents from 12 years of age for the treatment of CMV disease in immunocompromised patients.[21]
- GCV is indicated in adults and adolescents from 12 years of age for the prevention of CMV disease in patients with drug-induced immunosuppression (for example following organ transplantation or cancer chemotherapy).[21]
- VGCV is indicated for the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.[22]

Clinical Trial Information

Trial	**SHP620-302,** NCT02927067, 2015-004726-34**;** A Phase 3, Multicenter, Randomized, Double-blind, Double-dummy, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Compared to Valganciclovir for the Treatment of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant Recipients **Phase III -** Recruiting **Location(s):** 9 EU countries, UK, Canada, USA and other countries. **Primary completion date:** May 2022
Trial Design	Randomised, parallel assignment, double-blind

Population	N = 550 (estimated), current CMV infection as the first episode of CMV viremia after HSCT, aged 16 years and older
Intervention(s)	Participants will receive 400 mg of maribavir twice daily orally along with a placebo matched to valganciclovir
Comparator(s)	Participants will receive valganciclovir tablets orally along with a placebo matched to maribavir.
Outcome(s)	Primary outcomes; • Proportion of Participants With Confirmed Clearance of Plasma CMV DNA (CMV Viremia Clearance) at the End of Study Week 8, Regardless of Whether Study Assigned Treatment was Completed [Time Frame: Week 8] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT00223925; A Randomized, Double-blind, Placebo-controlled, Dose-ranging Study to Assess the Safety, Tolerability, and Prophylactic Anti-cytomegalovirus Activity of Maribavir in Recipients of Allogeneic Stem Cell Transplants **Phase II -** Completed **Location(s):** USA **Study completion date:** April 2006
Trial Design	Randomised, parallel assignment, double-blind
Population	N = 111, CMV seropositive, allogeneic stem cell transplant recipient, aged 18 years and older
Intervention(s)	• Maribavir (100 mg twice daily) • Maribavir (400 mg twice daily) • Maribavir (400 mg once daily)
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes; • Clinical safety as measured by the recording of treatment emergent adverse events [Time Frame: 13 weeks] See trial record for full list of other outcomes.
Results (efficacy)	Within the first 100 days after transplantation, the incidence of CMV infection based on CMV pp65 antigenemia was lower in each of the respective maribavir groups (15%, *P* = .046; 19%, *P* = .116; 15%, *P* = .053) compared with placebo (39%). Similarly, the incidence of CMV infection based on plasma CMV DNA was lower in each of the respective maribavir groups (7%, *P* = .001; 11%, *P* = .007; 19%, *P* = .038) compared with placebo (46%). Anti-CMV therapy was also used less often in patients receiving each respective dose of maribavir (15%, *P* = .001; 30%, *P* = .051; 15%, *P* = .002) compared with placebo (57%).[23]

Results (safety)	There were 3 cases of CMV disease in placebo patients but none in the maribavir patients. Adverse events, mostly taste disturbance, nausea, and vomiting, were more frequent with maribavir. Maribavir had no adverse effect on neutrophil or platelet counts.[23]

Estimated Cost

The cost of maribavir is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Maribavir for treating refractory or resistant cytomegalovirus infection after transplant (GID-TA10792). Expected publication date: 14 September 2022.
- NICE technology appraisal. Letermovir for preventing cytomegalovirus disease after a stem cell transplant (TA591). July 2019.

NHS England (Policy/Commissioning) Guidance

- NHS England Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT) (All Ages). B04/P/a.

Other Guidance

- European Conference on Infections in Leukaemia (ECIL 7). Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). 2019.[24]
- British Society for Haematology Guidelines. Management of cytomegalovirus infection in haemopoietic stem cell transplantation. 2013.[10]

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