Amsterdam, 23 February 2023
EMA/112993/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Livtencity

Maribavir

Procedure no.: EMA/H/C/005787/P46/002

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

On 12 December 2022, the MAH submitted a final CSR of study SHP620-302 in accordance with Article 46 of Regulation (EC) No1901/2006. Study SHP620-302 is part of maribavir Paediatric Investigational Plan (EMEA-000353-PIP02-16-M02) and includes data from adolescents.

A Clinical Overview Addendum has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study SHP620-302 was a double-blind, randomised, double-dummy, active-controlled trial to evaluate pharmacokinetics, safety, efficacy of maribavir compared to valganciclovir for the treatment of asymptomatic CMV infection in adolescent and adult haematopoietic stem cell transplant (HSCT) recipients. Since adolescents have been included in this study, this study is part of maribavir Paediatric Investigational Plan (EMEA-000353-PIP02-16-M02). Furthermore, study SHP620-302 was included in the RMP to address the potential risk of serious adverse reactions due to an increase in immunosuppressant drug level.

In this assessment report (AR), only data from adolescents investigated during study SHP620-302 are assessed in detail. Results of the overall study are only summarised for overview.

2.2. Information on the pharmaceutical formulation used in the study

During study SHP620-302 maribavir 200 mg tablets were used (same formulation in adults and adolescents).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final Clinical Study Report (CSR) for:

- Study SHP620-302, a double-blind, randomised, double-dummy, active-controlled trial to evaluate pharmacokinetics, safety, and efficacy of maribavir compared to valganciclovir for the treatment of asymptomatic CMV infection in adolescent and adult haematopoietic stem cell transplant (HSCT) recipients.

2.3.2. Clinical study

Clinical study number and title

Study SHP620-302 was a double-blind, randomised, double-dummy, active-controlled trial to evaluate pharmacokinetics, safety, and efficacy of maribavir compared to valganciclovir for the treatment of asymptomatic CMV infection in adolescent and adult haematopoietic stem cell transplant (HSCT) recipients.

Description

This was a Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled study of maribavir compared to valganciclovir for the treatment of asymptomatic CMV infection in HSCT

recipients. “Asymptomatic subjects” were defined as HSCT recipients who did not have tissue-invasive CMV disease at baseline.

All eligible subjects were stratified based on:

1. Prebaseline viral load as determined by the local or central specialty laboratory quantitative polymerase chain reaction (qPCR):

- high viral load: whole blood CMV deoxyribonucleic acid (DNA) ≥27300 IU/mL or plasma CMV DNA ≥9100 IU/mL
- low viral load: whole blood CMV DNA ≥2730 IU/mL to <27300 IU/mL or plasma CMV DNA ≥910 IU/mL to <9100 IU/mL
- very low viral load: whole blood CMV DNA <2730 IU/mL or plasma CMV DNA <910 IU/mL (in subjects with high-risk infection); and by

2. Acute graft-versus-host disease (GVHD) status (presence or absence at baseline). Subjects in each stratum were then randomized in a 1:1 allocation ratio to receive double-blind maribavir (400 mg twice daily [BID]) or valganciclovir (either 900 mg BID, 450 mg BID, or 450 mg once daily [QD], based on subject's creatinine clearance at eligibility) for 8 weeks. The dose of valganciclovir was allowed to be adjusted during the study for renal function impairment or neutropenia.

Methods

Study participants

This was a study in adults allowing inclusion of male and female adolescents from 16 to less than 18 years of age, weighing at least 40 kg, with asymptomatic CMV infection after HSCT.

A subject was not considered eligible for the study without meeting all of the criteria below:

- Was a recipient of HSCT.
- Had a documented asymptomatic CMV infection, with a screening value of CMV DNA ≥1365 IU/mL to ≤273000 IU/mL in whole blood or ≥455 IU/mL to ≤91000 IU/mL in plasma in 2 consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory qPCR or comparable quantitative CMV DNA results. Both samples were to be taken within 14 days prior to randomization, with second sample obtained within 5 days prior to randomization. Same laboratory and same sample type (whole blood or plasma) were to be used for these assessments. Asymptomatic CMV infection was defined as an infection that did not present with tissue-invasive CMV disease, as assessed by the investigator.
- Subjects with CMV DNA <910 and ≥455 IU/mL in plasma or <2730 and ≥1365 IU/mL in whole blood had to meet at least 1 of the following criteria for high-risk CMV infection to be eligible:
    - Human leukocyte antigen (HLA)-related (sibling) donor with at least 1 mismatch at 1 of the following 3 HLA-gene loci: HLA-A, -B or -DR,
    - Haploidentical donor,
    - Unrelated donor with at least 1 mismatch at 1 of the following 4 HLA –gene loci: HLA-A, -B, -C and -DRB1,
    - Use of umbilical cord blood as stem cell source,
    - Use of ex vivo T-cell–depleted grafts,

    - Grade 2 or greater GVHD, requiring the use of systemic corticosteroids (defined as the use of ≥1 mg/kg/day of prednisone or equivalent dose of another corticosteroid).
- Had the current CMV infection as the first episode of CMV viremia after HSCT, either primary or reactivation, which in the investigator's opinion required treatment.
- Per investigator's judgment, was eligible for treatment with valganciclovir.
- Had all of the following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory could have been used for qualification):
    - ANC ≥1000/mm3 (1.0×109/L)
    - Platelet count ≥25,000/mm^3 (25×10^9/L)
    - Hemoglobin ≥8 g/dL
- Estimated creatinine clearance ≥30 mL/min
- Was able to swallow tablets
- Had life expectancy of ≥8 weeks
- Weighed ≥40 kg

A subject was excluded from the study if any of the following criteria were met. Subjects must not have:

- Had CMV tissue-invasive disease as assessed by the investigator at the time of screening and randomization at Visit 2/Day 0.
- Had a CMV infection that was known to be genotypically resistant to ganciclovir, valganciclovir, foscarnet, or cidofovir based on documented evidence.
- Presented with recurrent CMV infection (defined as a new detection of CMV infection in a subject who had at least one previously documented episode of CMV infection posttransplant, and who had at least 2 weeks of undetectable CMV DNA between the episodes during active surveillance, based on same local laboratory and same sample type). The subject must also have been off any anti-CMV treatment between the current and prior infection. Otherwise, the current infection may have been considered continuation of the prior infection.
- Required ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment was initiated (example: herpes simplex virus co-infection that required use of any of these agents after the randomization) or needed a co-administration with maribavir for CMV infection.
- Received leflunomide, letermovir, or artesunate when study treatment was initiated. Note: Subjects who were receiving leflunomide must have discontinued the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Subjects who received letermovir must have discontinued use 3 days prior to the first dose of study treatment. Subjects who received artesunate must have discontinued the use prior to the first dose of study treatment.
- Had been on treatment with anti-CMV agents (ganciclovir, valganciclovir, foscarnet, or letermovir) for the current CMV infection for longer than 72 hours.
- Had known hypersensitivity to the active substance or to an excipient of the study treatments.

- Had severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would have precluded administration of oral medication.
- Required mechanical ventilation or vasopressors for hemodynamic support at the time of randomization.
- Was female and pregnant or breast feeding.
- Had previously completed, discontinued, or had been withdrawn from this study.
- Had received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time.
- Had received any unapproved agent or device within 30 days before initiation of study treatment.
- Had any clinically significant medical or surgical condition that, in the investigator's opinion, could have interfered with interpretation of study results, contraindicated the administration of the assigned study treatment, or compromised the safety or well-being of the subject.
- Had previously received maribavir.
- Had serum aspartate aminotransferase >5 times upper limit of normal (ULN) at screening, or serum alanine aminotransferase >5 times ULN at screening, or total bilirubin $\geq 3.0 \times$ ULN at screening (except for documented Gilberts syndrome), as analyzed by local or central laboratory.
- Had known (previously documented) positive results for human immunodeficiency virus (HIV). Subjects must have had a confirmed negative HIV test result within 3 months of study entry or, if unavailable, be tested by a local laboratory during the screening period.
- Had active malignancy with the exception of nonmelanoma skin cancer, as determined by the investigator. Subjects who experienced relapse or progression of their underlying malignancy (for which HSCT was performed), as determined by the investigator, were not to be enrolled.
- Had received treatment for acute or chronic hepatitis C.

Treatments

Maribavir 200 mg tablets were orally administered at 400 mg BID for 8 weeks. The control group received valganciclovir (450 mg QD to 900 mg BID as adjusted for renal function, based on chemistry labs at screening) for the 8 weeks of the study treatment phase.

Objectives

The primary objective of the study was:

- To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance at the end of Study Week 8 in asymptomatic CMV infection in hematopoietic stem cell transplantation (HSCT) recipients.

The key secondary objective of the study was:

- To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved at the end of Study Week 8 through Study Week 16 (8 weeks of posttreatment/follow-up phase).

The secondary objectives of the study were:

- To compare the efficacy of maribavir to valganciclovir in CMV viremia clearance after completion of 8 weeks of treatment for asymptomatic CMV infection in HSCT recipients.
- To compare the efficacy of maribavir and valganciclovir on maintenance of CMV viremia clearance, achieved after completion of 8 weeks of treatment, through Study Weeks 12 (4 weeks of posttreatment period), 16 (8 weeks of posttreatment/follow-up phase), and 20 (12 weeks posttreatment).
- To assess the maintenance of CMV viremia clearance, achieved at the end of Study Week 8, through Weeks 12 (4 weeks of posttreatment period), and 20 (12 weeks posttreatment).
- To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment groups during the first 8 weeks of the study, during the 12 weeks of the follow-up study phase, and at any time during the study.
- To evaluate the incidence of recurrence of confirmed CMV viremia in the 2 study treatment groups when subjects are on treatment and off treatment.
- To evaluate the incidence of treatment-emergent grade 3 or 4 neutropenia (defined as absolute neutrophil count [ANC] <1000/mm^3 or ANC <500/mm^3) while on treatment.
- To assess the safety and tolerability of maribavir compared to valganciclovir.
- To characterize the pharmacokinetics (PK) of maribavir.

Outcomes/endpoints

The primary efficacy endpoint (a binary response) was confirmed clearance of plasma CMV DNA (confirmed CMV viremia clearance) at the end of Study Week 8. Subjects who received alternative, non-study anti-CMV treatment prior to Study Week 8 were considered non-responders regardless of viral load.

The key secondary endpoint was a binary response (yes/no) with the following criteria:

- Achievement of clearance of viremia at the end of Study Week 8 (virologic response) and no clinical findings of CMV tissue-invasive disease at the end of Study Week 8 (CMV infection symptom control), followed by maintenance of this treatment effect for an additional 8 weeks off treatment (ie, through Week 16).

Sample size

Approximately 550 subjects were planned to be randomized (275 subjects in the maribavir group and 275 subjects in the valganciclovir control group). In this adult study it was allowed to include male and female adolescents from 16 to less than 18 years of age, weighing at least 40 kg, with asymptomatic CMV infection after HSCT.

Randomisation and blinding (masking)

This was a randomized, double-blind, double-dummy, active-controlled study.

Statistical Methods

Efficacy: The primary efficacy analysis was based on the Modified Randomized Set, with Per Protocol Set as supportive. For binary endpoints (responder or non-responders), the difference in proportion of

responders between treatment groups was obtained using Cochran-Mantel-Haenszel (CMH) weighted average across strata, and tested using CMH method, with baseline plasma CMV DNA concentration levels and presence or absence of acute GVHD as the stratification factors. The 95% confidence intervals (CIs) of the weighted average of difference across strata were provided using the normal approximation. If the lower limit of the 95% CI is greater than -7%, it was to be concluded that maribavir is as efficacious as valganciclovir.

The hypothesis testing of the primary and key secondary efficacy endpoints was adjusted for multiple comparisons using a gatekeeping testing procedure to control the family-wise Type 1 error rate at 2-sided α=5% level. The testing was done in the order of primary efficacy endpoint noninferiority (NI) testing first, the primary efficacy endpoint superiority testing and the key secondary efficacy endpoint NI testing second, and lastly the key secondary efficacy endpoint superiority testing.

First, the NI hypothesis of the primary efficacy endpoint (H11) was tested based on the 2-sided 95% CI of the adjusted difference in proportion of subjects who had CMV viremia clearance at Study Week 8 stratified by baseline CMV DNA level and presence/absence of acute GVHD at baseline. If the lower limit of the 95% CI was above -7%, NI of the primary efficacy endpoint was considered established, ie, H11 was rejected.

If and only if after the NI of the primary efficacy endpoint was established, ie, H11 was rejected, the superiority hypothesis of the primary efficacy endpoint (H12) and the NI hypothesis of the key secondary endpoint of maintenance of response through Study Week 16 (H21) were tested in parallel. The Hochberg procedure was used to control family-wise Type 1 error rate at the 2-sided α=5% level.

If and only if the superiority of the primary efficacy endpoint and NI of key secondary efficacy endpoint were established, ie, H12 and H21 were both rejected, the superiority hypothesis of the key secondary efficacy endpoint (H22) was tested based at the 2-sided 0.05 level.

Other secondary endpoints are summarized and analyzed similarly without adjustment of multiplicity.

Results for recurrence endpoints were reported as the number (%) of subjects with recurrence in the designated study period.

Safety: The Safety Set consisted of all subjects who received at least 1 dose of study drug. All safety analyses were performed using the Safety Set in the on-treatment period and the overall study period unless otherwise specified. Summary statistics were provided to evaluate all safety endpoints by treatment groups. No statistical tests for comparisons of treatment groups were performed for safety endpoints.

Pharmacokinetics: The PK Set included all subjects who took any dose of maribavir and had plasma sample drawn and tested for maribavir concentrations. Based on sparse PK sampling, minimum observed concentration (Cmin) was estimated for each subject at each PK visit and average Cmin was calculated for each subject. Maribavir concentrations were listed and summarized by treatment and visit. The C_{min} and average Cmin were listed and summarized.

For adolescent subjects, in addition to analysis on C_{min}, other PK parameters at Week 1 were also calculated by standard noncompartmental analysis (NCA) method.

Results

A total of 4 adolescents were enrolled and randomized to Study SHP620-302: 1 subject in the maribavir group and 3 subjects in the valganciclovir group. All subjects were 17 years old.

Overall, 553 subjects were randomized into Study SHP620-302 (549 adults, 4 adolescents) and 319 (57.7%) randomized subjects completed 8 weeks of study-assigned treatment.

A higher percentage of subjects in the maribavir group (64.9%) compared to the valganciclovir group (50.5%) completed the 8-week treatment period. The most frequent reasons for treatment discontinuation in the maribavir group and valganciclovir group included: adverse events which was higher in the valganciclovir group (23.9% and 38.3%, respectively), lack of efficacy (5.1% and 3.6%, respectively), and other (2.2% and 3.6%, respectively). Treatment discontinuations due to death were infrequent, occurring in 1.1% of maribavir-treated subjects and 0.4% for valganciclovir-treated subjects.

Efficacy results

The one adolescent who received maribavir during Study SHP620-302 was not considered as a responder as the subject discontinued the study after 9 days of treatment.

Overall, in Study SHP620-302 maribavir did not achieve NI to valganciclovir on the primary endpoint of confirmed viremia clearance at Week 8. However, at all the post-treatment evaluations at Weeks 12, 16 and 20, maribavir CMV viremia clearance and symptom control rates were comparable to (and numerically higher than) valganciclovir. Post-treatment recurrence was higher in the valganciclovir group, explaining the numeric advantage of maribavir at the later endpoints. Conversely, recurrence while on study-treatment was higher in the maribavir group and usually associated with the development of resistance to maribavir.

For the primary endpoint, 190 (69.6%) subjects in the maribavir group and 212 (77.4%) subjects in the valganciclovir group achieved confirmed CMV viremia clearance at Week 8. The adjusted difference in the proportions of responders (maribavir vs. valganciclovir) was -7.7% (95% CI: -14.98, -0.36; p=0.040). The criteria for NI of maribavir to valganciclovir for the primary endpoint was not met because the lower limit of the 95.0% CI around the treatment difference exceeded -7.0.

For the key secondary efficacy endpoint of viremia clearance and symptom control at Week 8 with maintenance of treatment effect through Week 16, the results were numerically comparable between subjects treated with maribavir (52.7%) and those treated with valganciclovir (48.5%). The adjusted treatment difference (95% CI) in proportion of responders between the treatment groups was 4.4 in favor of maribavir (-3.91, 12.76), p=0.298.

Safety results

No TEAE was reported for the one adolescent who received maribavir during Study SHP620-302.

Overall, in Study SHP620-302 maribavir was well tolerated and demonstrated an acceptable safety profile and had fewer treatment-limiting adverse events than valganciclovir:

- A lower proportion of subjects in the maribavir group (27.8%) discontinued study medication due to a TEAE compared to the valganciclovir group (41.2%).
- The median duration of exposure based on the difference between last and first dose date regardless of dose withheld was similar between the 2 groups (56 days [range: 1, 62] in the maribavir group and 54 days [range: 2, 63] in the valganciclovir group). The median duration of actual exposure after taking dose interruption/withholding into consideration was higher in the maribavir group than the valganciclovir group (54 days [range: 1, 62] and 46 days [range: 1, 60], respectively). The percentage of subjects who had dose change requests was lower in the maribavir group than the valganciclovir group (29.7% vs 44.5%, respectively), with

neutropenia the primary reason for valganciclovir dose change (maribavir: 6.2%; valganciclovir: 27.4%).

- The incidence of TEAEs, severe TEAEs, deaths, and SAEs was similar between treatment groups.

2.3.3. Discussion on clinical aspects

Only four adolescent subjects age ≥16 to <18 years were enrolled in Study SHP620-302 of which just one patient received maribavir. This was a 17-year-old subject who was not considered as a responder as the subject discontinued the study after 9 days of treatment. According to the Opinion of the Paediatric Committee on the acceptance of a modification of an agreed PIP (EMEA-000353-PIP02-16-M02) at least 4 adolescents evaluable for the primary analysis with a randomization ratio of 1:1 should have been included into Study SHP620-302. However, finally only one adolescent was included into the maribavir group and three adolescents in the comparator group. The one adolescent who received maribavir was a non-responder and no TEAE was reported for this patient. However, based on data from one adolescent no conclusion is possible regarding the efficacy and safety of maribavir in this population. Furthermore, the meaningfulness of PK data from one patient is also questionable. Accordingly, no update of the SmPC is proposed.

Overall, Study SHP620-302 did not achieve NI to valganciclovir on the primary endpoint of confirmed viremia clearance at Week 8.

3. Rapporteur's overall conclusion and recommendation

Only four adolescent subjects age ≥16 to <18 years were enrolled in Study SHP620-302 of which only one patient received maribavir. The one adolescent who received maribavir was a non-responder and no TEAE was reported for this patient. However, based on data from one adolescent no conclusion is possible regarding the efficacy and safety of maribavir in this population. Furthermore, the meaningfulness of PK data from one patient is also questionable. Accordingly, no update of the SmPC is proposed by the MAH, which is agreed. As outlined in the Opinion of the Paediatric Committee on the acceptance of a modification of an agreed PIP (EMEA-000353-PIP02-16-M02) Study TAK-620-2004 is planned to evaluate PK, safety, tolerability antiviral activity and acceptability of maribavir for the treatment of CMV infection in children and adolescents from birth to less than 18 years of age who have received a HSCT which will be the main column for the question if data from adults can be extrapolated to children and adolescents.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

N/A