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Preliminary Dosing for Adolescent Hematopoietic Stem Cell Transplant Recipients Based on Pharmacokinetic, Efficacy, and Safety Data of Letermovir for Cytomegalovirus Prophylaxis

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Background

- Cytomegalovirus (CMV) seropositivity and reactivation are associated with increased morbidity and mortality in recipients of allogeneic hematopoietic stem cell transplant (HSCT)[1-3]
- The CMV terminase complex inhibitor, letermovir, reduced the risk of clinically significant CMV infection through Week 24 post-transplant when compared with placebo and was associated with a favorable safety profile in adult CMV-seropositive allogeneic HSCT recipients (R+) in a Phase 3 trial (P001).[4] Letermovir was subsequently approved for prophylaxis of CMV infection and disease in adult R+ allogeneic HSCT recipients[5]
  - The mechanism of action of letermovir contrasts with that of CMV DNA polymerase inhibitors, which are subject to cross-resistance[6] and limited in their use due to myelosuppression and nephrotoxicity[7]
- Although there are few published data, clinical manifestations of CMV disease appear to be similar in adults and children,[8] and letermovir is expected to have a similar efficacy and safety profile in pediatric and adult populations when administered at doses that achieve exposures observed in adult populations; however, no pharmacokinetic (PK) data are currently available for letermovir in pediatric patients
- The pharmacokinetics, efficacy, safety, and tolerability of letermovir for CMV prophylaxis in pediatric allogeneic HSCT recipients from birth to <18 years of age are being assessed in an ongoing Phase 2b study
  - Here we report preliminary study results from participants aged 12 to <18 years

Methods

Study Design and Participants

- This is a Phase 2b, open-label, multicenter, single-arm study (NCT03940586) in participants from birth to <18 years of age at risk of developing CMV infection and/or disease following allogeneic HSCT
- Participants are divided into 3 age groups:
  - Age Group 1: 12 to <18 years
  - Age Group 2: 2 to <12 years
  - Age Group 3: birth to <2 years
- Key inclusion criteria for Age Group 1 participants:
  - Recipient of first allogeneic hematopoietic stem cell transplant (bone marrow, peripheral blood stem cell, or cord blood) within 28 days prior to enrollment
  - Recipient documented as seropositive for CMV IgG within 90 days prior to enrollment
  - Documented absence of CMV viremia by DNA polymerase chain reaction (PCR) from a sample collected within 5 days prior to enrollment
- Key exclusion criteria for Age Group 1 participants:
  - CMV end-organ disease within 6 months prior to enrollment
  - Treatment with ganciclovir, valganciclovir, foscarnet, acyclovir, valacyclovir, or famciclovir within 7 days prior to enrollment
  - Previous treatment with letermovir
- Participants (or their legally acceptable representative) provided written informed consent. The study was reviewed and approved by the appropriate institutional review board or independent ethics committee at each center

Study Procedures

- All Age Group 1 participants were screened from up to 15 days prior to transplant to 28 days post-transplant, including weekly confirmation of absence of CMV viremia by DNA PCR prior to enrollment (**Figure 1a**)
- Participants were enrolled within 28 days post-transplant
- Participants received the recommended daily adult dose of 480 mg letermovir (adjusted to 240 mg with concomitant cyclosporin A [CsA] administration) through Week 14 post-transplant, based on physiologically based pharmacokinetic (PBPK) and population PK modeling that suggested the adult dose would result in letermovir exposures in this age group comparable to adults
- Oral administration was preferred, with intravenous (IV) administration only in participants who could not tolerate oral intake (e.g., due to vomiting or gastrointestinal graft-versus-host disease)
- Participants were followed through Week 24 post-transplant for efficacy and through Week 48 post-transplant for safety and tolerability

Pharmacokinetic Exposure Targets

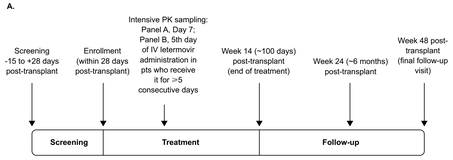
- Steady-state median target range for area under the concentration-time curve from 0 to 24 hours post-dose (AUC0–24), predicted in adult HSCT recipients from the Phase 3 population PK model[9] following administration of oral and IV letermovir 480 mg daily without CsA: **34,400 – 100,000 h.ng/mL**
  - Lower bound of adult HSCT exposure range: 16,900 h.ng/mL (5th AUC0–24 percentile following 480 mg oral letermovir)
  - Upper bound of adult HSCT exposure range: 148,000 h.ng/mL (95th AUC0–24 percentile following 480 mg IV letermovir)
- The sequence of PK evaluation is shown in **Figure 1b**

Endpoints

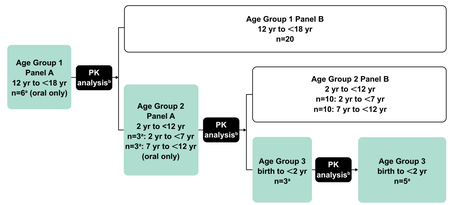
PK endpoints

- Steady-state AUC0–24 for letermovir (non-compartmental analysis; per-protocol population)
- Maximum plasma concentration (Cmax) for participants receiving the oral formulation (concentration at the end of infusion [Ceoi] for participants receiving the IV formulation)
- Time to Cmax (Tmax)
- Half-life (t½)

Figure 1. (a) Study design and (b) sequential pharmacokinetic evaluation of age groups



Intensive PK sampling was performed pre-dose and 1, 2.5, 8, and 24 hours post-dose.
Sparse PK sampling took place at Weeks 2, 4, 6, 8, 10, 12, and 14 post-transplant during the treatment phase.



IV, intravenous; PK, pharmacokinetic
[a]Number of PK-evaluable participants
[b]PK analysis occured at 3 intervals: when all evaluable participants had completed intensive PK in Age Group 1 Panel A, when all evaluable participants had completed intensive PK in Age Group 2 Panel A, and when the first 3 evaluable participants had completed intensive PK in Age Group 3. The final dose selected in Panel A simultaneously triggered initiation of Panel B for the same age group and Panel A for the next youngest age group. The use of CsA and IV administration of letermovir were permitted in Panel B.

Efficacy endpoint

- Proportion of participants with clinically significant CMV infection (CS-CMVi) through Weeks 14 and 24 post-transplant:
  - CS-CMVi was defined as the onset of CMV end-organ disease adjudicated by an independent committee, and/or initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viremia and the participant's clinical condition
  - The primary missing data approach will be Non-Completer = Failure (NC=F). A participant who had missing efficacy measures at the study time point (e.g., Week 24 post-transplant) will be considered a failure
  - The primary efficacy population was the full analysis set (FAS) population, defined as all participants who received ≥1 dose of study intervention and had no detectable CMV viral DNA on Day 1 of treatment

Safety assessments

- Safety and tolerability through Week 48 post-transplant
  - The primary safety population was the all-participants-as-treated (APaT) population, defined as all participants who received ≥1 dose of study intervention

Results

Participant Disposition and Baseline Characteristics

- Participant disposition is shown in **Table 1**. All 28 participants enrolled in Age Group 1 received study medication, and 17/28 (60.7%) completed treatment

Table 1. Disposition of participants

Participants, n (%)	Age Group 1 (N=28)
Treated	28 (100.0)
Completed study medication	17 (60.7)
Discontinued study medication	11 (39.3)
Adverse event	5 (17.9)
Lack of efficacy	5 (17.9)
Withdrawal by parent or guardian	1 (3.6)
Completed study	21 (75.0)
Discontinued study	7 (25.0)
Death	3 (10.7)
Withdrawal by parent or guardian	3 (10.7)
Physician decision	1 (3.6)

- Participant demographics and baseline characteristics are shown in **Table 2**. Three (10.7%) participants had detectable CMV DNA on Day 1 of study treatment and were not included in the primary efficacy analysis. The most common conditions necessitating transplant were acute myeloid leukemia (in 6 [21.4%] cases), aplastic anemia (4 [14.3%] cases), and recurrent acute lymphocytic leukemia (3 [10.7%] cases)

Table 2. Baseline demographic and clinical characteristics (all participants as treated)

Parameter	Age Group 1 (N=28)
Median (range) age, years	13.5 (12–17)
Median (range) body weight, kg	53.8 (28.7–95.0)
Sex, n (%)	
Male	15 (53.6)
Female	13 (46.4)
Race, n (%)	
White	15 (53.6)
Asian	6 (21.4)
Black or African American	3 (10.7)
Mixed	4 (14.3)
Ethnicity, n (%)	
Hispanic or Latino	9 (32.1)
Not Hispanic or Latino	14 (50.0)
Not reported	4 (14.3)
Unknown	1 (3.6)
Region, n (%)	
Europe and Middle East	9 (32.1)
Asia-Pacific	8 (28.6)
North America	6 (21.4)
Latin America	5 (17.9)
Immunosuppressive regimen, n (%)	
CsA[a]	19 (67.9)
Tacrolimus[b]	9 (32.1)
Other[c]	0 (0.0)
CMV DNA on Day 1 of study treatment, n (%)	
Detected	3 (10.7)
Not detected	25 (89.3)
Donor CMV serostatus, n (%)	
CMV-seropositive	20 (71.4)
CMV-seronegative	8 (28.6)
Recipient CMV-seropositive, n (%)	28 (100.0)
Donor type, n (%)	
Matched related	6 (21.4)
Mismatched related	9 (32.1)
Matched unrelated	9 (32.1)
Mismatched unrelated	4 (14.3)
Haploidentical donor, n (%)	
Yes	8 (28.6)
No	20 (71.4)
Stem cell source, n (%)	
Peripheral blood	15 (53.6)
Bone marrow	12 (42.9)
Cord blood	1 (3.6)
Conditioning regimen, n (%)	
Myeloablative	25 (89.3)
Reduced intensity	3 (10.7)

CMV, cytomegalovirus; CsA, cyclosporin A.
[a]Co-administered with letermovir during the treatment phase with or without other immunosuppressants
[b]Regimen containing tacrolimus alone or with any other immunosuppressants except CsA
[c]Regimen containing any immunosuppressants except CsA or tacrolimus

Pharmacokinetics

- Of the 13 PK-evaluable participants in Age Group 1 (body weight, 30.4–87.7 kg), 8 received oral or IV 480 mg QD letermovir without CsA, and 5 received oral or IV 240 mg QD letermovir with CsA. PK parameters for letermovir are summarized in **Table 3**
  - Of the 8 participants who received letermovir without CsA (oral, n=5; IV, n=3), 6 achieved exposures within the bounds of the adult HSCT exposure range, including 5 within the median target range, and 2 (oral, n=1; IV, n=1) achieved exposures above the upper bound of the adult HSCT exposure range, but lower than the maximum observed in the Phase 1 letermovir program (**Figure 2**)
  - All 5 participants who received letermovir with CsA (oral, n=1; IV, n=4) achieved exposures within the bounds of the adult HSCT exposure range, including 3 participants within the median target range
  - No dose modifications were necessary based on interim PK analysis

Efficacy

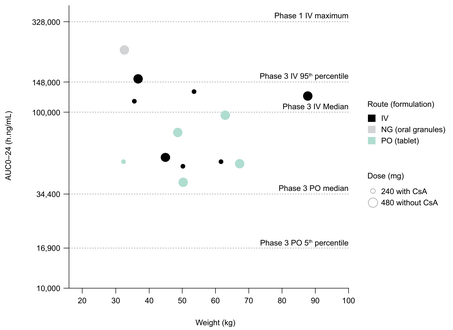
- Of the 25 efficacy-evaluable Age Group 1 participants, there were 5 (20%) failures (participants who developed CS-CMVi, prematurely discontinued from the study, or had missing data at the visit window) through Week 14 post-transplant, and 6 (24%) failures through Week 24 post-transplant (**Table 4**)
- Pre-emptive therapy was initiated for 2 (8%) participants due to documented CMV viremia through Week 24 post-transplant; no participants had documented CMV end-organ disease

Table 3. Pharmacokinetic parameters for letermovir in Age Group 1 participants who underwent intensive pharmacokinetic sampling

Letermovir regimen	Route	n	AUC0–24 (h.ng/mL) GM (GCV, %)	Cmax (ng/mL)[a] GM (GCV, %)	Tmax (h), median (min, max)	t½ (h), GM (GCV, %)
480 mg QD alone	Oral	5[b]	80,300 (75.0)	7,420 (70.1)	5.85 (2.38, 8.00)	5.48 (26.3)
	IV	3	102,000 (58.4)	24,700 (49.4)	–	6.22 (39.8)
240 mg QD with CsA	Oral	1[c]	52,100	2,600	2.52	38.0
	IV	4	78,800 (54.6)	13,600 (48.2)	–	8.28 (40.2)

AUC0–24, area under the curve from administration to 24 hours post-dose; Cmax, maximum plasma concentration; GCV, geometric coefficient of variation; GM, geometric mean; IV, intravenous; max, maximum; min, minimum; PK, pharmacokinetic; QD, once daily; t½, half-life; Tmax, time to maximum plasma concentration
[a]For the IV route, the Cmax is the concentration at the end of the 1-hour infusion
[b]Includes 4 participants who received tablets and 1 participant who received oral granules via nasogastric tube
[c]This participant received a 240 mg tablet

Figure 2. Individual letermovir exposures in Age Group 1 participants who underwent intensive pharmacokinetic sampling.



AUC0–24; area under the concentration-time curve from administration to 24 hours post-dose (logarithmic scale); CsA, cyclosporin A; IV, intravenous; NG, nasogastric tube; PO, oral; Phase 1 PO maximum, highest AUC0–24 observed in Phase 1 letermovir program.

Table 4. Proportion of participants with clinically significant CMV infection through Week 14 and Week 24 post-transplant (Full Analysis Set population[a])

Parameter, n (%)	Age Group 1 (N=25)	
	Visit window	
	Week 14 post-transplant	Week 24 post-transplant
Failures[b]	5 (20.0)	6 (24.0)
CS-CMVi[c] through visit window	2 (8.0)	2 (8.0)
Initiation of PET based on documented CMV viremia	2 (8.0)	2 (8.0)
CMV end-organ disease	0 (0.0)	0 (0.0)
Discontinued from study before visit window	2 (8.0)	4 (16.0)
Missing outcome in visit window	1 (4.0)	0 (0.0)

CMV, cytomegalovirus; CS-CMVi, clinically significant CMV infection; PET, pre-emptive therapy.
[a]Primary efficacy population, defined as all allocated participants who received ≥1 dose of study intervention and had no detectable CMV viral DNA on Day 1 of treatment
[b]Categories of failure are mutually exclusive and listed in hierarchical order. With the non-completer=failure approach, failure was defined as all participants who developed CS-CMVi, prematurely discontinued from the study, or had a missing outcome through the post-transplant visit window
[c]Defined as proven or probable CMV end-organ disease, or initiation of PET based on documented CMV viremia and the participant's clinical condition

Safety

- The most common AEs were vomiting (14 [50%] cases), nausea (12 [42.9%] cases), diarrhea (12 [42.9%] cases), abdominal pain (11 [39.3%] cases), and pyrexia (11 [39.3%] cases). AEs with incidence ≥5% are summarized in **Table 5**
- Nine (32.1%) participants experienced ≥1 AE assessed as being drug-related by investigators. The most common drug-related AEs were those related to gastrointestinal disorders, including vomiting (4 [14.3%] cases) and nausea (1 [3.6%] case)
- There were three deaths, all in Age Group 1, due to:
  - (i) Candida infection and multiple organ dysfunction syndrome,
  - (ii) Post-transplant lymphoproliferative disorder and hepatosplenic candidiasis, and
  - (iii) Recurrent acute myeloid leukemia
  - None of these were considered to be drug-related by the investigators

Table 5. Participants with adverse events during treatment phase (incidence ≥5 participants for individual preferred terms; All Participants as Treated[a])

Participants, n (%)	Age Group 1 (N=28)
With ≥1 AE[b]	28 (100)
Gastrointestinal disorders	27 (96.4)
Vomiting	14 (50.0)
Nausea	12 (42.9)
Diarrhea	12 (42.9)
Abdominal pain	11 (39.3)
Stomatitis	8 (28.6)
General disorders and administration site conditions	16 (57.1)
Pyrexia	11 (39.3)
Immune system disorders	15 (53.6)
Graft-versus-host disease	10 (35.7)
Renal and urinary disorders	14 (50.0)
Dysuria	6 (21.4)
Nervous system disorders	13 (46.4)
Headache	6 (21.4)
Respiratory, thoracic, and mediastinal disorders	13 (46.4)
Oropharyngeal pain	5 (17.9)
Skin and subcutaneous tissue disorders	12 (42.9)
Pruritus	6 (21.4)
Vascular disorders	10 (35.7)
Hypertension	7 (25.0)
Blood and lymphatic system disorders	8 (28.6)
Thrombocytopenia	5 (17.9)

AE, adverse event
[a]Primary safety population, defined as all allocated participants who received ≥1 dose of study intervention
[b]AEs were reported using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1. Each participant was counted once for each system organ class or specific AE

Conclusions

- Administration of adult doses of letermovir for CMV prophylaxis post-transplant in adolescents aged 12 to <18 years resulted in exposures within the prespecified bounds of the adult HSCT exposure range
- The efficacy of letermovir in prevention of CS-CMVi in adolescents through Week 24 post-transplant was comparable to that reported in adults in the pivotal Phase 3 trial[4]
- No major safety concerns were reported with letermovir among the adolescent participants in this study
- Although the results of the present study are preliminary and should not be interpreted as dose recommendations, they support the use of 480 mg QD (240 mg if co-administered with CsA) as the dosing regimen for letermovir in adolescent HSCT recipients

References

1. Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol*. 2016;3(3):e119–e127.
2. Schmidt-Hieber M, Labopin M, Beelen D, et al. CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. *Blood*. 2013;122(19):3359–3364.
3. Ljungman P, Schmitt M, Marty FM, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis*. 2020;70(8):1525–1533.
4. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic–cell transplantation. *N Engl J Med*. 2017;377(25):2433–2444.
5. Merck Sharp & Dohme LLC, Rahway, NJ, USA. Prevymis™ prescribing information. Available at: https://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_pi.pdf.
6. El Helou G, Razonable RR. Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients: an evidence-based review. *Infect Drug Resist*. 2019;12:1481–1491.
7. Hakki M. Moving past ganciclovir and foscarnet: Advances in CMV Therapy. *Curr Hematol Malig Rep*. 2020;15(2):90–102.
8. Castagnola E, Cappelli B, Erba D, Rabagliati A, Lanino E, Dini G. Cytomegalovirus infection after bone marrow transplantation in children. *Hum Immunol*. 2004;65(5):416–422.
9. Prohn M, Viberg A, Zhang D, et al. Population pharmacokinetics of letermovir following oral and intravenous administration in healthy participants and allogeneic hematopoietic cell transplantation recipients. *CPT Pharmacometrics Syst Pharmacol*. 2021;10(3):255–267.

Disclosures

Andreas Groll has received research support from Gilead Sciences, Merck Sharp & Dohme, and Pfizer; is a consultant for Amplyx, Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp & Dohme, and Pfizer; and served at the speakers' bureau of Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp & Dohme, and Pfizer. Johannes H. Schulte is supported by the German Cancer Consortium (DKTK). Ali Bülent Antmen is a consultant for Novo Nordisk, Pfizer, Roche, and Takeda. Christopher J. Fraser has no potential conflicts of interest to declare. Valerie L. Teal, Barbara Haber, Luzelena Caro, Jacqueline B. McCrea, Karsten Menzel, and Cyrus Badshah are current employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. Craig Fancourt is a former employee of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA.

Acknowledgments

The authors thank all study participants, investigators, and contributors.

Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Mayankbhai V. Patel supported the development of Figure 2.

Medical writing assistance, under the direction of the authors, was provided by Ajay Mirakhur, MPH, of CMC AFFINITY, a division of IPG Health Medical Communications, in accordance with Good Publication Practice (GPP 2022) guidelines. This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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Presented at IDWeek; Washington, D.C., USA; October 19–23, 2022.