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| **Official Protocol Title:** | A Phase 3 Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of Letermovir (LET) Prophylaxis When Extended From 100 Days to 200 Days Post-Transplant in Cytomegalovirus (CMV) Seropositive Recipients (R+) of an Allogeneic Hematopoietic Stem Cell Transplant (HSCT) |
| **NCT number:** | NCT03930615 |
| **Document Date:** | 25-Apr-2022 |

# Supplemental Statistical Analysis Plan (sSAP)

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# 1 INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

# 2 SUMMARY OF CHANGES

The following changes are summarized in detail in later sections of this document.

- Clarification of allowable lab collection date for PET
- Clarification of event counting when both PET initiation and an event of CMV disease confirmed by Clinical Adjudication Committee occur in the same participant
- Time to non-relapse mortality added as an exploratory endpoint
- Relative day ranges for efficacy endpoints and safety endpoints
- No missing data approach for all-cause mortality
- Further details for sensitivity analyses

# 3 ANALYTICAL AND METHODOLOGICAL DETAILS

## 3.1 Statistical Analysis Plan Summary

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| **Study Design Overview** | A Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET) prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT) |
| **Treatment Assignment** | Approximately 216 participants who have already received ~100 days of LET will be randomized in a 2:1 ratio with 144 receiving LET prophylaxis for an additional 100 days (200-day arm) and 72 receiving placebo (100-day arm). Treatment allocation / randomization will be stratified by study center and haploidentical donor (yes/no). |
| **Analysis Populations** | Efficacy: Full Analysis Set (FAS)<br>Safety: All Participants as Treated (APaT) |
| **Primary Endpoint(s)** | Proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant |

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| **Key Secondary Endpoints** | 1. Safety and tolerability of LET<br>2. Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant and from Week 14 post-transplant through Week 48 post-transplant<br>3. Time to clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant<br>4. Proportion of participants with PET for documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant<br>5. Proportion of participants with of all-cause mortality from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant<br>6. Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant |
| **Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses** | The primary hypothesis will be evaluated by comparing LET to placebo with respect to the proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant using the stratified Mantel-Haenszel method [Koch, G. G., et al 1990] when LET prophylaxis is extended from 100 to 200 days post-transplant. |
| **Statistical Methods for Key Safety Analyses** | 95% CIs (Tier 2 endpoints) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985]. |
| **Interim Analyses** | Periodic safety analyses will be conducted for the accruing data and will be reviewed by an external Data Monitoring Committee (DMC) at regular intervals as outlined in the DMC charter. This will supplement routine in-house medical monitoring. No formal interim analyses for efficacy are planned for this study. However, efficacy data will be included as part of the periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment to allow for an assessment of benefit-risk. |

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| **Multiplicity** | No formal efficacy analyses will be provided and there is no intention of stopping the trial due to overwhelming efficacy at any of these safety reviews. Nevertheless, since unblinded efficacy data are being periodically reviewed, using a Haybittle-Peto α spending approach, a small amount of alpha ($\alpha = 0.0001$) will be allocated for each of these looks before testing the primary efficacy hypothesis at Week 28 post-transplant. An allowance will be made such that a total of up to three of these unblinded efficacy reports may be presented at these periodic safety reviews. The final analysiscan still be tested at 2.5% level without inflating Type-I error. |

## 3.2 Responsibility for Analyses/In-House Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor. This study will be conducted as a double-blind study under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule for study treatment assignment. Randomization will be implemented in the IRT.

Blinding issues related to the planned interim analyses are described in Section 9.7 of the protocol.

## 3.3 Hypotheses/Estimation

Objectives of the study are stated in Section 3 of the protocol.

## 3.4 Analysis Endpoints

### 3.4.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 4.2.1.1.

The primary efficacy endpoint will be the proportion of participants with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28(~200 days) post-transplant, defined as the occurrence of either one of the following outcomes:

- onset of CMV end-organ disease (proven or probable)

  OR

- initiation of anti-CMV PET with approved anti-CMV agents (ganciclovir, valganciclovir, foscarnet, and/or cidofovir) based on documented CMV viremia andthe clinical condition of the participant.

CMV end-organ disease will be determined using the definitions in Appendix 7 of the protocol and confirmed by an independent, blinded CAC. The adjudication of cases by the CAC (ie, the final CAC assessment) will take precedence over the investigator's assessment for the purpose of analysis. Only the CAC-confirmed (proven or probable) cases of CMV end-organ disease will be included in the CMV end-organ disease category. However, investigator-assessed CMV end-organ disease cases that were not confirmed by the CAC but in whom anti-CMV therapy was initiated (in the setting of documented CMV viremia at a central laboratory) will be included in the initiation of PET category and, therefore, qualify as havingclinically significant CMV infection. Concordance/discordance between CAC and investigator assessment will be summarized.

Documented viremia is defined as any quantifiable CMV viral DNA on a confirmatory sample obtained immediately prior to (i.e., on one day before or on the day of) the initiation of treatment for CMV disease or PET, as measured by the Roche COBAS® AmpliPrep/ COBAS TaqMan® (CAP/CTM) System in the central laboratory. In the event that the confirmatory result is not available, a subsequent central laboratory result collected from a sample obtained within 7 days will be used. Initiation of anti-CMV therapy without documented CMV viremia (using the central laboratory) will not be considered as a case for clinically significant CMV infection. Similarly, quantifiable CMV viral DNA alone without initiation of anti-CMV therapy will not be considered as a case for clinically significant CMV infection. If there are cases where anti-CMV therapy is initiated with no quantifiable CMV viral DNA using the central laboratory data, a sensitivity analysis will be provided using the local laboratory results.

When both PET initiation and an event of CMV disease confirmed by adjudication occur in a subject, the following rules on counting these events for the endpoint analyses will be implemented.

- If PET is initiated greater than 2 weeks before the onset date of the adjudicated CMV end-organ disease, then PET and CMV end-organ disease are both counted as endpoint events. Time to event for the primary endpoint will be relative days from start of transplantation to the onset of PET. For individual events, it will be relative to start of transplantation to the onset of the respective event.

- If PET is initiated within 2 weeks before onset of the adjudicated CMV end-organ disease or PET is initiated after onset of the adjudicated CMV end-organ disease, then PET is not counted as an endpoint event. Time to event for the primary endpoint will be relative days from start of transplantation to the onset of the adjudicated CMV end-organ disease.

The secondary efficacy endpoints are:

1. Proportion of participants with clinically significant CMV infection from Week 14post-transplant through Week 38 post-transplant and from Week 14 post-transplantWeek 48 post-transplant. This endpoint will use the same definition of clinically significant CMV infection as in the primary efficacy endpoint.

   Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant and from Week 14 post-transplant through Week 48 post-transplant.

   The time to onset of clinically significant CMV infection will be calculated in days, from the day of transplant to the day of onset of CMV end-organ disease or to the day of initiation of anti-CMV PET. For cases where CMV end-organ disease is confirmed by the CAC, date of the first diagnostic test (including, but not limited to, radiology tests, viral culture, histopathology, immunohistochemical analysis, in situ hybridization, and CMV DNA PCR) will be identified by the CAC as part of their medical review and used as the time of onset of CMV end-organ disease. For cases where anti-CMV PET is initiated in the setting of documented viremia (including those applicable cases where CMV end-organ disease was not confirmed by the CAC), the start date of anti-CMV therapy will be used. If both criteria for clinically significant CMV infection are met, the time to onset will be calculated from the day of transplant to the earlier day on which one of the criteria is met.

2. Proportion of participants with initiation of PET for documented CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant. This endpoint will use the same definition for initiation of PET for documented CMV viremia as in the primary efficacy endpoint.

3. Proportion of participants with all-cause mortality from Week 14 post-transplant through post-Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

4. Time to all-cause mortality from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant. The time to all-cause mortality will be calculated in days, from the day of transplant to the day of death.

### 3.4.2 Safety Endpoints

An initial description of safety measures is provided in Sections 8.3 and 8.4.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory values and vital signs. All AEs will be collected through 14 days after completion of treatment period. Thereafter, all drug-related SAEs and SAEs leading to death will be collected through Week 48 post-transplant.

### 3.4.3 Exploratory Endpoints

1. Proportion of participants with CMV end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

2. Time to CMV end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant. The time to CMV end-organ disease will be calculated in days, from the day of transplant to the day of CMV end-organ disease.

3. Proportion of participants with documented CMV viremia ≥300 copies/mL from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

4. The time to documented CMV viremia ≥300 copies/mL from Week 14 post-transplant through Week 48 post-transplant.

5. Proportion of participants with select opportunistic infections other than CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

6. Proportion of participants with GVHD from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

7. Proportion of participants with all rehospitalizations and rehospitalizations for CMV infection/end-organ disease from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

8. Days on intravenous medications other than LET from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

9. Proportion of participants with recurrent CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant.

10. Proportion of participants with CMV-specific T cell responses (positive, indeterminate, or negative) as measured by the release of γ-interferon using the QuantiFERON-CMV assay.

11. Antiviral resistance to LET in prophylaxis failures.

12. The time to non-relapse mortality from Week 14 post-transplant through Week 48 post-transplant.

## 3.5 Analysis Populations

### 3.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this study. The FAS population consists of all randomized participants who received at least one dose of study treatment.

### 3.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the All Participants as Treated (APaT) population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter.

To assess change from baseline, a baseline measurement is also required.

## 3.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8. Nominal p-values may be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conductedat the $\alpha$=0.025 (1-sided) level.

### 3.6.1 Statistical Methods for Efficacy Analyses

**Time Window**

Table 1 lists the definition of time windows and the target relative day for the scheduled visits in the study which will be used for all analyses by timepoint. Where there are multiple measures within a window, the one closest to the target day will be used.

**Table 1 Definition of Study Timepoints for Efficacy Analyses**

| Treatment Phase | Protocol Time | Relative Day Ranges[a] | Target Relative Day[a] | CSR Time[b] |
|---|---|---|---|---|
| Pre-treatment | Day of Transplant | ≤1 | 1 | |
| Baseline / end of first 100 days | Day 1 | ≥93 to ≤107 | 100 | Baseline |
| End of Treatment | Week 28 Post-transplant | ≥183 to ≤210 | 197 | Week 28 Post-transplant |
| Post-treatment Follow-up 1 | Week 38 Post-transplant | ≥253 to ≤280 | 267 | Week 38 Post-transplant |
| Post-treatment Follow-up 2 | Week 48 Post-transplant | ≥323 to ≤350 | 337 | Week 48 Post-transplant |

[a] Relative days and target day are counted from the day of transplant.

[b] The clinical study report (CSR) time is the time point label to be used in the analysis tables.

## Missing Data Handling

There are three types of missing values:

- Intermittent missing values due to a missed or skipped visit.
- Monotone (non-intermittent) missing due to premature discontinuation from thestudy: viremia at study discontinuation.
- Monotone missing due to premature discontinuation from the study: no viremia at study discontinuation.

Table 2 provides a summary of approaches to handle missing values.

**Table 2 Summary of Approaches to Handle Missing Values for Viremia Endpoints**

| Approach | Intermittent Missing | Monotone Missing | |
|---|---|---|---|
| | | No Viremia at Study Discontinuation | Viremia at Study Discontinuation |
| OF | No failure | No failure | Failure |
| NC=F | Failure | Failure | Failure |
| DAO | Excluded | Excluded | Excluded |

F = failure; NC = Non-Completer; OF = Observed Failure; DAO = Data-As-Observed

The primary missing data approach will be the Observed Failure (OF) approach in order to obtain an estimate of the proportion of clinically significant CMV infection in participants who receive prophylaxis study treatment. Using this approach, participants who develop clinically significant CMV infection or participants who discontinue prematurely from the study with viremia will be counted as failures, and participants who discontinue prematurely from the study for any reason without viremia or those who are missing data at the time points of interest are not considered failures. Imputing all participants who discontinue from the study prematurely without viremia as failures is likely to substantially overestimate the proportion of participants with clinically significant CMV infection.

Two secondary missing data approaches will be used for supportive analyses. The first is the Data-As-Observed (DAO) approach. In the DAO approach, any participant with missing value for a particular endpoint, either because they discontinued from the study without the endpoint or are missing data at the key time point (eg, missed visit, missing lab value), will be excluded from the analysis. The second approach is the Non-Completer = Failure (NC=F) approach, which provides the worse-case scenario estimate of the proportion of clinically significant CMV infection. Non-completers refer to participants who prematurely discontinue from the study for any reason without having developed CMV infection or participants who are missing data at the time points of interest. These participants will be considered failures using the NC=F approach.

For all-cause mortality, vital status is collected at week 48 for those who discontinue from the study. The expectation is that this will result in minimal missing data for this endpoint. Only those documented deaths will be counted as events. (This is considered an OF approach to missing data as noted in Table 3).

**Primary Efficacy Analysis**

To test the primary hypothesis that LET is superior to placebo in the prevention of clinically significant CMV infection when LET prophylaxis is extended from 100 to 200 days post-transplant, the stratum-adjusted Mantel-Haenszel method (with continuity correction) will be used to compare the proportion of subjects with clinically significant CMV infection from Week 14 (~100 days) post-transplant through Week 28 (~200 days) post-transplant between the two treatment groups [Koch, G. G., et al 1990]. The stratification factor of haploidentical donor (yes/no) will be included in the primary efficacy analysis. Cochran Mantel-Haenszel weights will be used to calculate the overall between-group differences across strata. LET is concluded superior to placebo if 1-sided p-value is less than or equal to 0.0249 (see Section 9.8 for alpha adjustment). Due to the anticipated large number of study centers, study center will not be included as a stratification factor in the primary efficacy analysis but may be explored as a sensitivity analysis. The primary efficacy analysis will be performed on the FAS population. A sensitivity analysis excluding those subjects who had quantifiable CMV viral DNA on Day 1 will be provided. The primary missing data approachwill be the OF approach; supportive analyses using different missing data approaches will also be conducted (see Table 3).

Additional sensitivity analyses for the primary endpoint will be performed to assess:

1) the proportion of participants with either CMV disease or PET initiation based on CMV viremia ≥300 copies/mL (ie, participants who initiated PET without meeting the threshold will not be considered a case of CS-CMVi),

2) the proportion of participants with either CMV disease or CMV viremia of ≥300 copies/mL regardless of whether PET was initiated.

Since the use of a therapy with anti-CMV activity may confound the results of this study, an additional sensitivity analysis will be conducted in which participants who start a therapy with anti-CMV activity will be censored at the time they begin such therapy. Subjects with CS-CMVi prior to taking a therapy with anti-CMV activity will be classified as having CS-CMVi. Those who did not have CS-CMVi prior to taking a therapy with anti-CMV activity (including subjects who subsequently develop CS-CMVi) will be classified as not having CS-CMVi and censored at the time they started taking the anti-CMV therapy. This analysis will be accomplished two ways. In the first approach, these participants will be excluded from analysis. In the second approach, they will be treated as failures.

3) The proportion of participants with clinically significant CMV infection, including those who started any therapy with anti-CMV activity as failures.

4) The proportion of participants with either CMV disease or PET initiation based on CMV viremia including local lab results.

**Secondary Efficacy Analyses**

To assess the difference in the proportion of participants with the following secondary endpoints:

- clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant
- clinically significant CMV infection from Week 14 post-transplant through Week 48 post-transplant
- initiation of PET for documented CMV viremia from Week 14 post-transplantthrough Week 28 post-transplant
- initiation of PET for documented CMV viremia from Week 14 post-transplantthrough Week 48 post-transplant
- all-cause mortality from Week 14 post-transplant through Week 28 post-transplant
- all-cause mortality from Week 14 post-transplant through Week 48 post-transplant

Similar to the primary endpoint, 95% confidence interval for the difference in proportion between treatment groups will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by haploidentical donor (yes/no) [Koch, G. G., et al 1990]. A nominal p-value will be provided to assess the strength of evidence of the effect.

Time to onset of clinically significant CMV infection from Week 14 post-transplant through 28 weeks post-transplant and from Week 14 post-transplant through Week 48 post-transplant will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm and a nominal p-value for the between-arm difference in time to onset of clinically significant CMV infection will be provided using the stratified log-rank test stratified by haploidentical donor (yes/no). Observations will be censored at last assessment. Time to all-cause mortality from Week 14 post-transplant through 28 weeks post-transplant and from Week 14 post-transplant through Week 48 post-transplant will be estimated similarly.

## Table 3 Analysis Strategy for Key Efficacy Variables

| Endpoint/Variable (Description, Time Point) | Primary vs. Supportive Approach† | Statistical Method | Analysis Population | Missing Data Approach* |
|---|---|---|---|---|
| **Primary Endpoint** | | | | |
| Proportion of participants with clinically significant CMV infection from Week 14post-transplant through Week 28 post-transplant | P | Stratified M&H‡ | FAS | OF |
| | S | Stratified M&H‡ | FAS | DAO |
| | S | Stratified M&H‡ | FAS | NC=F |
| **Secondary Endpoints** | | | | |
| Proportion of participants with clinically significant CMV infection from Week 14 post-transplant through Week 38 post-transplant and from Week 14 post-transplant through Week 48 post-transplant | P | Stratified M&H‡ | FAS | OF |
| | S | Stratified M&H‡ | FAS | DAO |
| | S | Stratified M&H‡ | FAS | NC=F |
| Time to onset of clinically significant CMV infection from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant | P | Kaplan-Meier | FAS | Censored at last assessment |
| Proportion of participants with initiation of anti-CMV PET for CMV viremia from Week 14 post-transplant through Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant weeks | P | Stratified M&H‡ | FAS | OF |
| | S | Stratified M&H‡ | FAS | DAO |
| | S | Stratified M&H‡ | FAS | NC=F |
| Proportion of participants with all-cause mortality from Week 14 post-transplantthrough Week 28 post-transplant, and from Week 14 post-transplant through Week 48 post-transplant weeks | P | Stratified M&H‡ | FAS | OF |
| Time to all-cause mortality from Week 14post-transplant through Week 28 post-transplant, and from Week 14post-transplant through Week 48 post-transplant | P | Kaplan-Meier | FAS | Censored at last assessment |

† P=Primary approach; S=Supportive approach.

‡ Stratum-adjusted Mantel-Haenszel method with stratification by haploidentical donor (yes/no)

* OF=observed failure; DAO=data-as-observed; NC=F = non-completers equal failure

### 3.6.2 Statistical Methods for Safety Analyses

**Time Window**

Table 4 lists the definition of time windows and the target relative day for the scheduled visits in the study which will be used for all safety analyses by timepoint. Where there are multiple measures within a window, the one closest to the target day will be used.

**Table 4 Definition of Study Timepoints for Safety Analyses**

| Treatment Phase | Protocol Time | Relative Day Ranges | Target Relative Day | CSR Time[a] |
|---|---|---|---|---|
| Baseline | Day 1 (Baseline) | £1 | 1 | Day 1 |
| Treatment[b] | Week 16 | ³2 and £21 | 8 | Week 1 |
| | Week 18 | ³22 and £35 | 15 | Week 2 |
| | Week 20 | ³ 36 and £49 | 22 | Week 3 |
| | Week 22 | ³ 50 and £63 | 29 | Week 4 |
| | Week 24 | ³ 64 and £77 | 85 | Week 12 |
| | Week 26 | ³ 78 and £91 | 92 | Week 13 |
| | Week 28 | ³ 92 and £105 | 99 | Week 14 |
| Post-treatment Follow-up | Week 30 | ³204 and £217 | 113 | Week 16 |
| | Week 32 | ³ 218 and £231 | 127 | Week 18 |
| | Week 34 | ³ 232 and £245 | 141 | Week 20 |
| | Week 36 | ³ 246 and £259 | 155 | Week 22 |
| | Week 38 | ³ 260 and £273 | 169 | Week 24 |
| | Week 40 | ³ 274 and £287 | 225 | Week 32 |
| | Week 44 | ³ 288 and £315 | 281 | Week 40 |
| | Week 48 | ³ 316 | 337 | Week 48 |

[a] The clinical study report (CSR) time is the time label to be used in the analysis tables.
[b] In the treatment phase, relative days and target day are counted from the first day of study medication.
[c] In the post-treatment follow-up phase, relative days and target day are counted from the day of transplant.

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs measurements.

The analysis of safety results will follow a tiered approach (Table 5). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) and events that meet predefined limits of change (PDLCs) in laboratory, and vital signs parameters are either prespecified as “Tier 1” endpoints or will be classified as belonging to “Tier 2” or “Tier 3” based on the observed proportions of participants with an event.

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. Thereare no Tier 1 events for this protocol as LET has not been associated with any significant AEs that need to be characterized compared to placebo.

**Tier 2 Events**

Tier 2 parameters will be assessed via point estimates with 95% confidence intervalsprovided for differences in the proportion of participants with events (Miettinen and Nurminen [M&N] method) [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 8 participants in the 200-day arm or 2 participants in the 100-day arm exhibit the event; all other AEs and predefined limits of change will belong to Tier 3.

The thresholds of events were chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when fewer participants per group, respectively, experience events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded asa helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and safety parameters that meet predefined limits of change.

In addition to individual events that occur in 8 or more participants in the 200-day arm or2 participants in the 100-day arm, the broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, and discontinuation due to an AE will be considered Tier 2 endpoints.

**Tier 3 Events**

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. Only point estimates by treatment group are provided for Tier 3 safety parameters.

**Continuous Safety Measures**

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

**Table 5 Analysis Strategy for Safety Parameters**

| Safety Tier | Safety Endpoint | 95% CI for Treatment Comparison | Descriptive Statistics |
|---|---|---|---|
| Tier 2 | Any AE† | X | X |
| | Any Serious AE | X | X |
| | Any Drug-Related AE | X | X |
| | Any Serious and Drug-Related AE | X | X |
| | Discontinuation due to AE | X | X |
| | Specific AEs, SOCs, or PDLCs‡ (incidence ≥8 participants in the 200-day arm or ≥2 participants in the 100-day arm) | X | X |
| Tier 3 | Specific AEs, SOCs or PDLCs (incidence ≥1 participant in either arm) | | X |
| | Change from Baseline Results (Labs, Vital Signs) | | X |

95% CIs will be based on the method of [Miettinen, O. and Nurminen, M. 1985].

† Indicates broad AE category of the number of participants reporting any adverse event.

Note: AE=adverse event; CI =confidence interval; SOC=System Organ Class; PDLC=Pre-Defined Limit of Change;X = results will be provided.

### 3.6.3 Exploratory Analyses

Exploratory endpoints (continuous and binary) will be assessed via point estimates with 95% CIs provided for between-arm comparisons. For the two continuous outcomes of duration of all re-hospitalizations (following initial hospital discharge) and duration of re-hospitalizations for CMV infection, means and standard deviations will be reported by treatment group.

Time-to-event exploratory endpoints will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm.

## 3.7 Interim Analyses

Study enrollment is likely to be ongoing at the time of any interim analyses. Blinding to treatment assignment will be maintained at all investigational sites. The results of interim analyses will not be shared with the investigators prior to the completion of the study.

To supplement the routine safety monitoring outlined in this protocol, an external DMC will serve as the primary reviewer of the results of the interim analyses of the study and will make recommendations for discontinuation of the study or protocol modifications to the EOC (see Appendix 1; Section 10.1.4 [Committees Structure – Executive Oversight Committee]). No formal interim analyses for efficacy are planned for this study. However, to allow for an assessment of benefit-risk, efficacy data will be included as part of the periodic safety

reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment. The DMC will monitor the trial with suggested periodic reviews occurring approximately every 6 months. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to results at the treatment level in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician. Additional logistical details will be provided in the DMC charter.

Treatment-level results from the interim analysis will be provided to the DMC by the unblinded statistician. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the interim analyses.

## 3.8 Multiplicity

The DMC will be provided with unblinded descriptive summaries of the efficacy data at their periodic safety reviews when at least 40% of the participants have completed treatment or discontinued prior to completing treatment for an assessment of benefit-risk. No formal efficacy analyses will be provided and there is no intention of stopping the trial due to overwhelming efficacy at any of these safety reviews. Nevertheless, since unblinded efficacy data are being periodically reviewed, using a Haybittle-Peto α-spending approach, a small amount of alpha ($\alpha = 0.0001$) will be allocated for each of these looks before testing the primary efficacy hypothesis at Week 28 post-transplant. An allowance will be made such that a total of up to three of these unblinded efficacy reports may be presented at these periodic safety reviews. The final analysis can still be tested at 2.5% level without inflating Type-I error.

## 3.9 Sample Size and Power Calculations

### 3.9.1 Sample Size and Power for Efficacy Analysis

Data from P001 in participants who were in the high-risk stratum as defined in P001 were used to estimate the clinically significant CMV infection rates for this study, since these populations are similar between the two studies. The 100-day arm in this study is similar to those in the high-risk stratum on LET who completed treatment without any clinically significant CMV infection in P001, in which 20.5% had clinically significant CMV infection after completing treatment and through Week 24 post-transplant. This would be expected to be slightly higher through Week 28 post-transplant leading to an estimate of 22% for through Week 28 post-transplant in this study. The event rate for the 200-day arm is expected to be similar to the event rate at the end of LET treatment at Week 14 post-transplant for participants in the P001-defined high-risk stratum, which was 10.8% (11/102, including 4 participants who had discontinued LET due to AEs and then developed CS-CMVi). Since this study will enroll participants who will have already tolerated LET for 100 days, it is expected that a lower percentage of patients will discontinue treatment due to AEs, thus lowering the overall failure rate in the 200-day arm to ~8%.

This study will randomize a total of 216 participants (in a 2:1 ratio) with 144 in the LET (200-day) arm and 72 in the placebo (100-day) arm which will have 80% power at an overall one-sided, 2.5% alpha-level, to demonstrate the primary hypothesis that extending LET prophylaxis to 200 days post-transplant is superior to 100 days of LET prophylaxis post-transplant in the prevention of clinically significant CMV infection. This assumes incidence rates of CS-CMVi of 8% for LET (200-day arm) and 22% for placebo (100-day arm). The calculation is based on normal approximation by Pearson Chi-square test for proportion difference without continuity correction and is carried out using (SAS v9.4). The minimum criterion for success is that the upper bound of 95% CI of difference < 0. Given the assumed response rate in 200-day arm, this may occur when the observed difference between treatment groups is approximately -10% or smaller. Table 6 presents the power under various assumptions of rates in the two arms using the OF approach for missing data.

**Table 6 Power (%) Under Various Assumptions (With 144 Participants Randomized in 200-day Arm and 72 in 100-day Arm)**

| Rate in Placebo (100-day) Arm | Rate in LET (200-day) Arm | | | | | |
|---|---|---|---|---|---|---|
| | 6 | 7 | 8 | 9 | 10 | 11 |
| 18 | 76 | 67 | 58 | 49 | 39 | 31 |
| 20 | 85 | 78 | 70 | 62 | 53 | 44 |
| 22 | 91 | 86 | 80 | 73 | 65 | 57 |
| 24 | 95 | 92 | 88 | 82 | 76 | 69 |
| 26 | 97 | 65 | 93 | 89 | 84 | 79 |
| 28 | 99 | 98 | 96 | 94 | 90 | 86 |

### 3.9.2 Sample Size and Power for Safety Analysis

The probability of observing at least one of a particular AE in this study depends on the number of participants treated and the underlying percentage of participants with that AE in the study population. If the underlying incidence of a particular AE is 1% (1 of every 100 participants receiving the drug), there is a 52% chance of observing at least one of that particular AE among 72 participants in the placebo (100-day) arm or a 76% chance of observing at least one of that particular AE among 144 participants in the LET (200-day) arm. If no AE of that particular type are observed among the 144 participants in the LET (200-day) arm, this study will provide 95% confidence that the underlying percentage of participants with that particular AE is <2.5% (one in every 40 participants).

The estimate of and the upper bound of the 95% confidence interval for the underlying percentage of participants with a particular AE given various hypothetical observed number of participants with the AE are provided in Table 7. The calculation is based on the exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. 1934] and is carried out using SAS v9.4.

**Table 7 Estimate of Incidence of AEs and 95% Upper Confidence Bound Based onHypothetical Numbers of Participants with AEs**

| | Hypothetical Number of Participants withan AE (Estimate of Incidence, %) | 95% Upper Confidence Bound† |
|---|---|---|
| N=72 | 0 (0) | 5.0 |
| | 2 (2.8) | 9.7 |
| | 4 (5.6) | 13.6 |
| | 6 (8.3) | 17.3 |
| N=144 | 0 (0) | 2.5 |
| | 4 (2.8) | 7.0 |
| | 8 (5.6) | 10.7 |
| | 12 (8.3) | 14.1 |

† Based on the two-sided exact confidence interval of a binomial proportion (Clopper and Pearson, 1934).

## 3.10 Subgroup Analyses and Effect of Baseline Factors

To assess the consistency of the treatment effect across various subgroups, the estimate of the between-arm treatment effect (with a nominal 95% CI) for the primary efficacy endpoint will be tabulated and plotted within each category of the following classification variables:

- Age category (≤65 versus >65 years)
- Sex (female, male)
- Race (white, black, Asian, other)
- Systemic steroid exposure within 6 weeks prior to randomization (yes, no)
- Donor type (mismatched related, matched unrelated, mismatched unrelated)
- Haploidentical donor (yes, no)
- Cord blood (yes, no)
- T-cell depleted grafts (yes, no)
- Receipt of anti-thymocyte globulin (yes, no)

The consistency of the treatment effect will be assessed descriptively via summary statisticsby category for the classification variables listed above. Other clinically relevant variables may be identified for which additional subgroup analyses may be performed. Subgroup analyses will not be conducted in categories that have less than 10% of the participants in either LET or placebo group (ie, no estimate of treatment difference and confidence intervals will be provided).

### 3.11 Compliance (Medication Adherence)

Study medication data for LET (200-day arm) and placebo (100-day arm) will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes at least 1 dose. For a participant who is followed for the entire study period, the "Number of days Should be on Therapy" is the total number of days from randomization to the last scheduled day for treatment administration for that participant. For a participant who discontinued from the study medication, the "Number of days Should be on Therapy" is the total number of days from randomization to the date of the last dose of study medication.

For each participant, percent compliance will then be calculated using the following formula:

$$Percent\ Compliance = \frac{Number\ of\ Days\ on\ Therapy}{Number\ of\ Days\ Should\ be\ on\ Therapy} \times 100$$

Summary statistics will be provided on percent compliance by treatment group for the APaT population.

### 3.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary for the "Number of days on Therapy" by treatment group.

# 4 LIST OF REFERENCES


| | | |
|---|---|---|
| [Clopper, C. J. 1934] | Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934;26(4):404-13. | [03Y75Y] |
| [Koch, G. G., et al 1990] | Koch GG, Carr GJ, Amara IA, Stokes ME, Uryniak TJ. Statistical methodology in the pharmaceutical sciences. Berry DA. editor. New York: Marcel Dekker, Inc.; c1990. Chapter 13, Categorical data analysis; p. 389-473. | [04YBDZ] |
| [Miettinen, O. and Nurminen, M. 1985] | Miettinen O, Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26. | [03QCDT] |