Official Protocol Title:	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients
NCT number:	NCT03443869
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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 and 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 will be summarized in detail in later sections of this document.

- Clarification of primary endpoint
- Clarification of missing data in OF approach
- Added exploratory endpoint of eGFR<60 through Week 28
- Deleted exploratory endpoints through week 52 which require laboratory measurements not collected past Week 32
- Relative day ranges for efficacy endpoints and safety endpoints added
- Added details of analysis of exploratory endpoints
- Compliance calculation

3 ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Study Design Overview	A Phase III, Randomized, Double-Blind, Comparator-controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients
Treatment Assignment	This is a double-blind study with a 1:1 randomization ratio. Treatment allocation / randomization will be stratified by use or non-use of highly cytolytic anti-lymphocyte immunotherapy during induction.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Subjects as Treated (ASaT)
Primary Endpoint	Proportion of participants with adjudicated CMV disease through 52 weeks post-transplant
Key Secondary Endpoints	Proportion of participants with adjudicated CMV disease through 28 weeks post-transplant Time to onset of adjudicated CMV disease through 52 weeks post-transplant
Statistical Methods for Key Efficacy Analyses	For the primary hypothesis, LET will be considered non-inferior to VGCV if the upper bound of the two-sided 95% CI for the proportion of participants with adjudicated CMV disease for (LET minus VGCV) is no higher than 0.10 (non-inferiority margin).
Statistical Methods for Key Safety Analyses	For safety events, p-values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) for between-treatment differences in the percentage of participants with events will be calculated using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].
Interim Analyses	No interim analyses are planned for this study.
Multiplicity	Superiority for the primary hypotheses will be tested only if non-inferiority is demonstrated. Due to the principles of closed testing, no adjustment for multiplicity is required for the superiority test.
Sample Size and Power	The planned sample size is 600. For the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant, the trial has 90% power to demonstrate that LET is non-inferior to VGCV at an overall two-sided 5% alpha-level.

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. Certain specific analyses such as those for PK, pharmacogenetics, and QoL measures will be the responsibility of the appropriate departments 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 schedules: both the initial randomization for study treatment assignment and the second allocation schedule for IV dosing for those participants not on concomitant CsA. Randomization will be implemented in the IVRS.

3.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 4 of the protocol.

3.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment differences are listed below, followed by the descriptions of the derivations of selected endpoints.

3.4.1 Efficacy Endpoints

An initial description of efficacy measures is provided in Section 5.4.1.1 of the protocol.

The primary efficacy endpoint will be the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant. Adjudicated CMV disease cases are defined as those cases that are adjudicated by the clinical adjudication committee (CAC) as a "yes" to CMV disease. If the primary objective of non-inferiority is achieved, superiority of LET versus VGCV will be evaluated by comparing the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant.

CMV disease is defined as the presence of either CMV end-organ disease or CMV syndrome and will be confirmed by an independent, blinded CAC. Only CAC-confirmed ("adjudicated") cases will be included in number of participants who met the endpoint. Investigator assessed cases which are not confirmed by the CAC will not be included. Concordance/discordance between CAC and investigator assessment will be summarized.

Quantifiable CMV DNAemia is defined as any detected CMV (ie, with a numeric value and not including reporting of PCR results as "detected, not quantifiable") using the Roche COBAS® AmpliPrep/COBAS TaqMan® (CAP/CTM) assay, which will be performed by the central laboratory. CMV DNA test results obtained from an investigator site-specific laboratory will not be used to determine quantifiable CMV DNAemia. Quantifiable CMV DNAemia may be considered as a subset of CMV infection, which is defined as virus isolation or detection of viral proteins (antigens) or nucleic acid in any body fluid or tissue specimen. The relationship of CMV infection to CMV disease is discussed in Section 5.4.1.1.

The secondary efficacy endpoints are:

1. Proportion of participants with adjudicated CMV disease through 28 weeks post transplant

   For this endpoint, adjudicated CMV disease will be defined in the same way it is for the primary efficacy endpoint.

2. Time to onset of adjudicated CMV disease through 52 weeks post transplant

   The time to onset of adjudicated CMV disease will be calculated in days, from the day of randomization to the day of onset of CMV disease as determined by the CAC.

3.4.2 Safety Endpoints

Leukopenia and neutropenia (see Section 5.4.1.3 of the protocol) will be assessed by evaluating the proportion of participants who develop any of the following during the treatment phase. This is specified as a Tier 1 safety endpoint.

1. Report an adverse event of leukopenia
2. Experience total WBC count ≤3,500 cells/μL
3. Report an adverse event of neutropenia
4. Experience ANC ≤1,000 cells/μL

The following are specified as events of interest (Tier-2 safety endpoints):

1. Proportion of participants with any adverse event
2. Proportion of participants with any drug-related adverse event
3. Proportion of participants with any SAE
4. Proportion of participants with any adverse event which is both drug-related and serious
5. Proportion of participants who discontinue due to an adverse event
6. Proportion of participants who report a total WBC count ≤3,500 cells/μL
7. Proportion of participants who report ANC ≤1,000 cells/μL

All AEs will be collected through 14 days after completion of the treatment period. Thereafter, all SAEs related to study medication will be collected through Week 52.

In addition, proportion of male participants with meaningful changes of Inhibin B, FSH, and LH testosterone serum concentrations will be evaluated to monitor testicular function.

3.4.3 Exploratory endpoints

1. Proportion of participants with quantifiable CMV DNAemia through 28 weeks post transplant and 52 weeks post-transplant

2. Proportion of participants experiencing allograft dysfunction and/or rejection through 28 weeks post transplant and 52 weeks post-transplant

    a. Proportion of participants who experience a ≥20% decline in post transplant eGFR (using Modification of Diet in Renal Disease [MDRD] formula) from 4 weeks post transplant (baseline) through 28 weeks post transplant.

    b. Proportion of participants with eGFR<60 ml/min/1.73m2 from 4 weeks post transplant (baseline) through 28 weeks post transplant

    c. Proportion of participants who experience a biopsy-proven acute renal graft rejection through 28 weeks post transplant and 52 weeks post-transplant

    d. Proportion of participants who experience graft loss through 28 weeks post transplant and 52 weeks post-transplant

3. Proportion of participants who experience NODAT through 28 weeks post transplant and 52 weeks post-transplant

    Of the participants identified by the investigator as developing NODAT during the study, the study team will perform a confirmatory analysis of NODAT.

4. Selected health outcomes (in addition to NODAT, see above) as follows:

    a. Incidence of all-cause mortality through 28 weeks post transplant and 52 weeks post-transplant

    b. Incidence and duration of all re-hospitalizations (following initial hospital discharge) and re hospitalizations for CMV infection/disease through 28 weeks post transplant and 52 weeks post-transplant

    c. Incidence of select OIs (see Section 9.10.1) through 28 weeks post transplant and 52 weeks post-transplant

    d. Proportion of participants who report more than one use of any G-CSF within any consecutive 30-day period beginning on Day 1 of treatment through the end of the treatment period.

5. Antiviral resistance to LET in prophylaxis failures through 52 weeks post transplant (see Section 9.5.8.3 for details)

6. Glycoprotein B (gB) genotype of CMV in prophylaxis failures through 52 weeks post transplant (see Section 9.5.8.4 for details)

7. Genetic analyses (see Section 5.4.1.5 for details)

8. Patient-reported outcomes (EQ-5D and SF-36v2® scores)

9. Pharmacokinetic endpoints, including the evaluation of exposure-response relationships with selected efficacy and safety endpoints (reported in a separate Modeling and Simulation report; see Section 10.6.3.2 for details)

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

3.5 Analysis Populations

3.5.1 Efficacy Analysis Populations

Full Analysis Set (FAS)

The 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, are D+/R-, and had no detectable CMV viral DNA (measured by central laboratory) on Day 1.

Per Protocol (PP)

The PP population will serve as a supportive analysis population. The PP population excludes participants due to important deviations from the protocol that may substantially affect the results of the primary and secondary efficacy endpoints.

Potential violations that may result in the exclusion of a participant from the PP population include:

- Failure to reasonably adhere to the dosing schedule for the study medication
- Failure to comply with specific inclusion/exclusion criteria
- Use of a prohibited concomitant medication during the treatment period that may impact on the efficacy assessment

The final determination on protocol violations will be made prior to the final unblinding of the database and will be documented in a protocol violator memo.

Participants will be included in the treatment arm to which they are randomized for the analysis of efficacy data using both the FAS and PP populations.

3.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment arm corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most participants this will be the treatment arm to which

they are randomized. Participants who take incorrect study treatment for the entire treatment period will be included in the treatment arm 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 each specific 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 10.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 10.8, Multiplicity. Nominal p-values will 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 conducted at the α=0.05 (2-sided) level.

3.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

Primary Efficacy Analysis

To test the primary hypothesis that LET is non-inferior to VGCV in the prevention of CMV disease, the difference between the two treatment arms in the proportions of participants with adjudicated CMV disease through 52 weeks post-transplant and the associated two-sided 95% CI will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies [Koch, G. G., et al 1990]. LET will be concluded to be non-inferior to VGCV if the upper bound of the two-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET - VGCV) is no higher than 0.10.

Exposure to the lower LET IV dose (240mg without concomitant CsA) is not expected to impact the primary efficacy analysis. For subjects randomized to receive IV LET (including 240mg or 480mg without concomitant CsA and 240mg with concomitant CsA), the percentage of time exposed to IV LET is anticipated to be minimal. Efficacy of the LET IV 240 mg (with and without concomitant CsA) and LET IV 480 mg (without concomitant CsA) groups may be assessed in an exploratory manner.

The primary efficacy analysis will be performed on the FAS population, with the PP population considered a supportive approach. A sensitivity analysis including those participants who were assessed by the investigator to have CMV disease regardless of the CAC determination will be performed. An additional sensitivity analysis will be performed where any participant who discontinues study treatment but thereafter is started on CMV prophylaxis at the discretion of the investigator is considered a failure.

Provided non-inferiority is established, a hypothesis that LET is superior to VGCV in the prevention of CMV disease will be tested. The stratum-adjusted Mantel-Haenszel method (with continuity correction) will be used to compare the two treatment arms with respect to the proportion of participants with adjudicated CMV disease through 52 weeks post-transplant using the stratification factor of highly cytolytic anti-lymphocyte therapies. LET will be concluded to be superior to VGCV if the upper bound of the two-sided 95% CI for the difference in proportion of participants with adjudicated CMV disease (LET – VGCV) is less than 0.

Secondary Efficacy Analyses

To assess the difference in the proportion of participants with adjudicated CMV disease through 28 weeks post-transplant, similar to the primary endpoint the difference between arms and the associated 95% CI will be calculated using the stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies. Formal hypothesis testing will be done on this endpoint in the event that the second primary hypothesis of superiority is met.

Time to onset of adjudicated CMV disease through 52 weeks post-transplant will be estimated using the nonparametric Kaplan-Meier method. The Kaplan-Meier curve will be plotted by treatment arm and a p-value for the between arm difference in time to onset of adjudicated CMV disease will be provided using the stratified log-rank test with stratification by highly cytolytic anti-lymphocyte therapies. Observations will be censored at the time of discontinuation from the study, or at completion of the study.

Missing Data Handling

There are two types of missing values:

- Intermittent missing values due to a missed or skipped visit. Note that this does not applyto the primary endpoint which is at the end of the trial but only to those endpoints evaluated prior to 52 weeks post-transplant. Participants who had missing information at the end of the trial are monotone missing.

- Monotone missing due to premature discontinuation from the study.

Table 1 provides a summary of approaches to handle missing values.

Table 1 Summary of Approaches to Handle Missing Values

Approach	Intermittent Missing	Monotone Missing
NC = F	Failure	Failure
OF	No failure	No failure
F = failure; NC = non-completer; OF = observed failure.		

The primary missing data approach will be the Observed Failure (OF) approach. Using this approach, participants who discontinue prematurely from the study for any reason or are missing data at the timepoint are not considered failures.

The Non-Completer = Failure (NC = F) approach will be used as a supportive analysis. Non-completers refers to participants who prematurely discontinue from the study for any reason without having developed CMV disease. Using the NC = F approach, these participants will also be considered failures.

Additional analysis to evaluate the potential effect of violations in assumptions about the missing data may be performed.

Table 2 summarizes the key efficacy analyses.

Table 2 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable (Description, Timepoint)	Primary Versus Supportive Approach[†]	Statistical Method	Analysis Population	Missing Data Approach[*]
Primary Hypothesis/Endpoint				
Proportion of participants with adjudicated CMV disease through 52 weeks post-transplant	P	Stratified M&H [‡]	FAS	OF
	S	Stratified M&H [‡]	FAS	NC = F
	S	Stratified M&H [‡]	PP	OF
Secondary Endpoints				
Proportion of participants with adjudicated CMV disease through 28 weeks post-transplant	P	Stratified M&H [‡]	FAS	OF
	S	Stratified M&H [‡]	FAS	NC = F
Time to onset of adjudicated CMV disease through 52 weekspost-transplant	P	Kaplan-Meier	FAS	N/A

[†] P = Primary approach; S = Supportive approach.

[*] OF = observed failure; M&H = Mantel-Haenszel method; NC =F = non-completers equal failure; N/A = not applicable.

[‡] Stratum-adjusted Mantel-Haenszel method with stratification by highly cytolytic anti-lymphocyte therapies

Efficacy Time Window

Table 3 lists the definition of time windows and the target relative day for the scheduled visits in the study which will be used for all efficacy analyses by timepoint. Where there are multiple measures within a window, the one closest to the target day will be used.

Table 3 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	Day 1	≥1 to ≤7		Baseline
End of Treatment	Week 28	≥ 183 and ≤210	197	Week 28 Post-transplant
Post-treatment Follow-up 2	Week 52	≥ 351	365	Week 52 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.

3.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach (Table 4). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% CIs provided for between-arm comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-arm comparisons; only point estimates by treatment arm are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change (PDLC) in laboratory parameters that are not pre-specified as Tier 1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 participants in any treatment arm exhibit the event; all other adverse experiences and PDLC will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% CI for the between-arm difference in percent incidence will always include zero when treatment arms of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-arm differences in adverse experiences and PDLC.

P-values (Tier 1 only) and 95% CIs (Tier 1 and Tier 2) 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 - an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985] and will not be stratified. All AEs will be analyzed through the end of the treatment period. Drug-related SAEs which are collected throughout the study will also be analyzed through Week 52.

Continuous measures such as changes from baseline in laboratory, vital signs, and ECG parameters that are not pre-specified as Tier-2 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 4 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Reporting any of the following: AE of leukopenia, total WBC count ≤3,500 cell/µL,AE of neutropenia, ANC ≤1,000 cell/µL	X	X	X
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 ≥4 participants in one of the treatment arms)		X	X
	Total WBC count ≤3,500 cell/µL		X	X
	ANC ≤1,000 cells/µL		X	X
Tier 3	Specific AEs, SOCs or PDLCs (incidence <4 participants in both treatment arms)			X
	Change from baseline results (laboratories, ECGs,vital signs)			X

AE = adverse event; ANC = absolute neutrophil count; CI = confidence interval; ECG = electrocardiogram; SOC = System Organ Class; PDLC = predefined limit of change; WBC = white blood cell; X = results will beprovided.

Time Window for Safety Analyses

Table 5 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 5 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 1	>1 and ≤11	8	Week 1
	Week 2	≥12 and ≤21	15	Week 2
	Week 4	≥22 and ≤35	29	Week 4
	Week 6	≥ 36 and ≤49	43	Week 6
	Week 8	≥ 50 and ≤63	57	Week 8
	Week 10	≥ 64 and ≤77	71	Week 10
	Week 12	≥ 78 and ≤98	85	Week 12
	Week 16	≥ 99 and ≤126	113	Week 16
	Week 20	≥ 127 and ≤154	141	Week 20
	Week 24	≥ 155 and ≤182	169	Week 24
	Week 28	≥ 183 and ≤210	197	Week 28
Post-treatment Follow-up[c]	Week 32	≥ 211 and ≤238	225	Week 32
	Week 36	≥ 239 and ≤266	253	Week 36
	Week 40	≥ 267 and ≤294	281	Week 40
	Week 44	≥ 295 and ≤322	309	Week 44
	Week 48	≥ 323 and ≤350	337	Week 48
	Week 52	≥351	365	Week 52

[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.

3.6.3 Statistical Methods for Exploratory Analyses

Exploratory endpoints will be assessed via point estimates with 95% CIs provided for between-arm comparisons. For continuous outcomes means and standard deviations will be reported by treatment group.

For the endpoint of proportion of participants with quantifiable CMV DNAemia through 28 weeks post-transplant and 52 weeks post-transplant, the primary analysis will be performed using central lab data. A supporting analysis will be done including local lab data.

For the endpoint of 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, point estimates and 95% CIs will also be provided by those with and without the primary endpoint.

Patient reported outcomes

Two patient-reported outcome measures were used in this study. The EQ-5D measures Health Related (HR)QoL on five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a 20-cm vertical visual analog scale (VAS) that generates a self-rating of HRQoL. The SF-36 (SF-36v2®) measure consists of eight scaled scores, which are in turn use to calculate two combined scores: the mental component summary (MCS) and physical component summary (PCS). Means and standard deviations for the scores and change from baseline will be provided by treatment group for the VAS score from the EQ-5D and for both the MCS and PCS for the SF-36.

3.6.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses Demographic and Baseline Characteristics

3.6.4.1 Demographic and Baseline Characteristics

The comparability of the treatment arms for each relevant characteristic will be assessed by the use of descriptive statistics. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized, and the primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, indication for kidney transplant, transplant and dialysis or plasmapheresis details (see Section 9.1.6), and prior and concomitant therapies will be summarized by treatment arm using descriptive statistics for continuous or categorical variables, as appropriate.

3.6.4.2 Pharmacokinetic Analyses

The PK data obtained from this study will be used to characterize the PK of LET in kidney transplant recipients and evaluate exposure-response relationships with selected efficacy and safety endpoints. The prospective details of this analysis will be specified in a separate Modeling and Simulation analysis plan.

3.7 Interim Analyses

No interim analyses for efficacy are planned for this study. However, to ensure safe study conduct, an independent unblinded external Data Monitoring Committee (DMC) will be established. The DMC will convene to review safety data approximately every 6 months during the study.

3.8 Multiplicity

The primary efficacy hypothesis for non-inferiority will be tested at a two-sided alpha level of 5% because no interim efficacy analyses will be performed. If the primary efficacy hypothesis testing for non-inferiority of LET is met, the second primary hypothesis of superiority will be tested at the two-sided Type I error rate of 5%. If the second primary hypothesis of superiority is met, similar step-down hypothesis testing will be performed for the secondary endpoint of adjudicated CMV disease through 28 weeks post-transplant. Other efficacy analyses will be considered secondary or explanatory.

3.9 Sample Size and Power Calculations

3.9.1 Sample Size and Power for Efficacy Analyses

Three hundred (300) participants will be randomized into each treatment arm for a total of 600 participants. Assuming the true proportion of participants with adjudicated CMV disease is 0.17 for both treatment arms, this study has 90% power to demonstrate that LET is non-inferior to VGCV at an overall two-sided 5% alpha-level, using a non-inferiority margin of 0.10. See section 5.4.1.1.3 for the rationale for the non-inferiority margin. The minimum criterion for success is that the upper bound of 95% CI of difference (LET minus VGCV) <0.10. The observed proportion of participants in the LET arm needs to be less than 4% higher than that in the VGCV arm in order to declare non-inferiority. If the observed proportion of participants in the LET arm is approximately 9% lower than in the VGCV arm, this is expected to demonstrate superiority with 90% power.

The adjudicated CMV disease incidence of 17% is supported by the results of the IMPACT study. In this study, the primary efficacy endpoint was the proportion of D+/R– participants who developed CMV disease (as defined in Appendix 7) adjudicated by the CAC.

3.9.2 Sample Size and Power for Safety Analyses

Table 6 summarizes the percentage point differences between the 2 treatment arms that could be detected with 90% probability for a variety of hypothetical underlying incidences of leukopenia (reported as AE) in the LET arm. These calculations assume 300 participants in each treatment arm and are based on a 1-sided 2.5% alpha level. The reported incidence of leukopenia AE in the IMPACT study is 38% for 200 days of VGCV [Humar, A., et al 2010]. The calculations are based on an asymptotic method proposed by Farrington and Manning (1990) [Farrington, C. P. and Manning, G. 1990].

Table 6 Power to Show Superiority for a Variety of Hypothetical Underlying Incidencesof Leukopenia Adverse Events (n = 300/arm)

	Power to Show Superiority with n=300/arm					
	LET Rate					
VGCV Response rate	18	20	22	24	26	28
30	93	81	61	<40	<40	<40
34	>99	97	91	78	57	<40
38	>99	>99	99	96	89	75
42	>99	>99	>99	>99	99	95
LET = letermovir; VGCV = valganciclovir						

3.10 Subgroup Analyses

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, non-white)
- Induction therapy (use, non-use of highly cytolytic, anti-lymphocyte immunotherapyduring induction)
- Region (US, Ex-US)

Other clinically relevant variables may be identified for which additional subgroup analyses may be performed.

Sample sizes within subgroups will be smaller than the overall trial sample size; therefore, estimation may not be precise and the 95% CIs may be wide. If any subgroup category has less than 15 participants in either treatment arm then only descriptive statistics will be displayed (no estimate of treatment difference and no CIs). If there are less than 15 participants in either treatment arm, the subgroup category will not be displayed in the forest plot.

3.11 Compliance (Medication Adherence)

Study medication data for LET, VGCV, ACV, and placebos will be collected during the study. A day within the study will be considered an "On-Therapy" day if the participant takes at least one 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. Dose days which are missed at the discretion of the investigator (physician's decision to titrate) will not count as "Number of Days Should be on Therapy". For a participant whodiscontinued 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:

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

Compliance rates will be summarized for each treatment arm and individual compliance rates will factor into the identification of protocol violators as discussed in Section 10.5.1.

3.12 Extent of Exposure

The extent of exposure of study treatment will be evaluated by summary statistics for the "Number of Days on Therapy" by treatment arm.

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