LETERMOVIR (MK-8228): OVERVIEW OF PIVOTAL PHASE 3 STUDY (P001) ASSESSING PROPHYLAXIS OF LETERMOVIR VS. PLACEBO IN ALLOGENEIC HSCT RECIPIENTS

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Letermovir (MK-8228): Background

Letermovir inhibits CMV through a novel mechanism involving the viral terminase complex

- Enzyme required for DNA cleavage into unit-length genome & packaging into procapsids

Potent CMV activity *in vitro* & *in vivo*

No cross-resistance with drugs currently used in treatment of CMV

- Drug resistance of letermovir mapped to UL56 subunit
- Resistance of other anti-CMV agents map to UL54 and/or UL97
- Lack of cross-resistance preserves treatment options for subjects who fail on letermovir

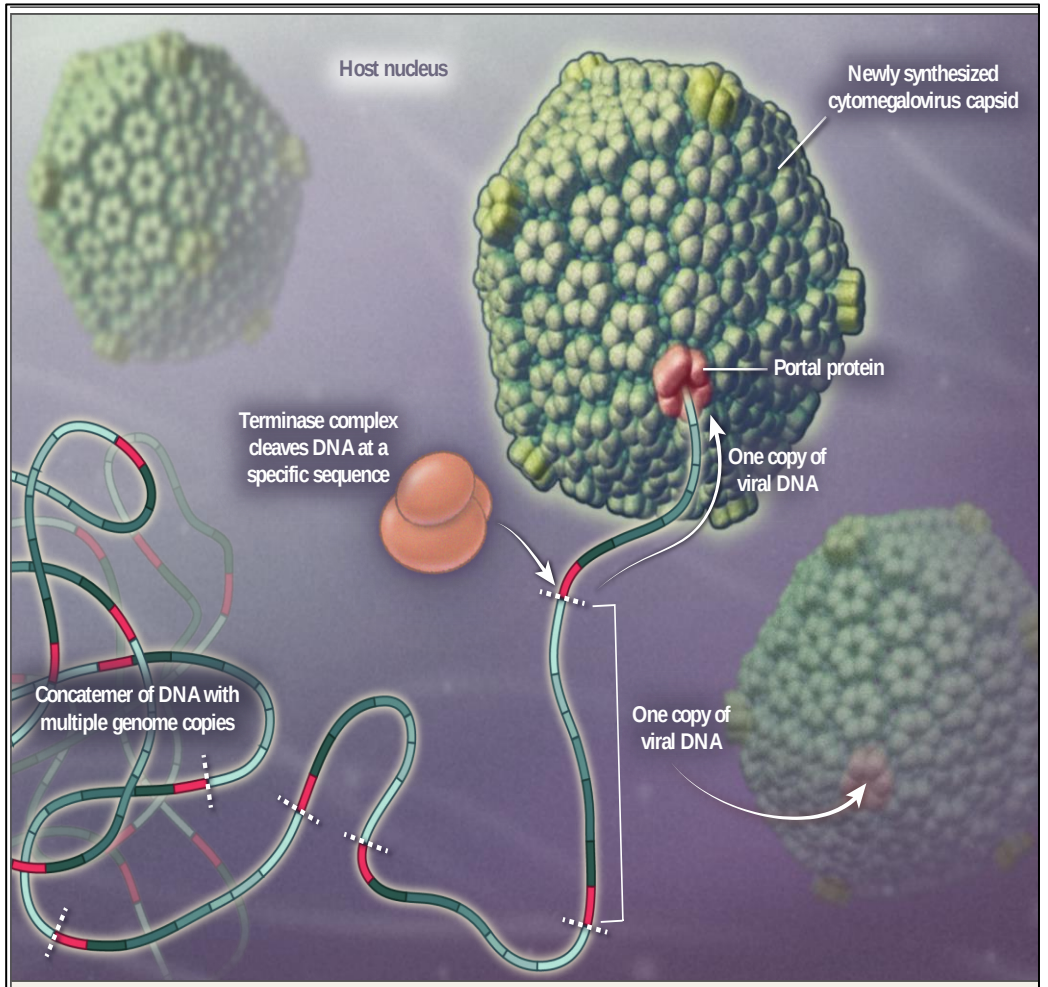

Figure 1. Structure of Cytomegalovirus.

Viral DNA, synthesized as a long, multiunit, concatemeric DNA molecule, is packaged into the capsid through a specialized portal protein that replaces one of the pentons in the icosahedral capsid. This packaging is an active process that consumes ATP. When the capsid is full, the terminase complex cleaves the DNA at specific sequences. The process is then repeated for another capsid. The long concatemeric DNA, which contains cleavage signals recognizable by the terminase complex, can be thought of as a train comprising individual identical coaches, each of which can be released when the terminase complex cleaves the couplings between them.

Figure courtesy of Griffiths & Emery, N Engl J Med 2014

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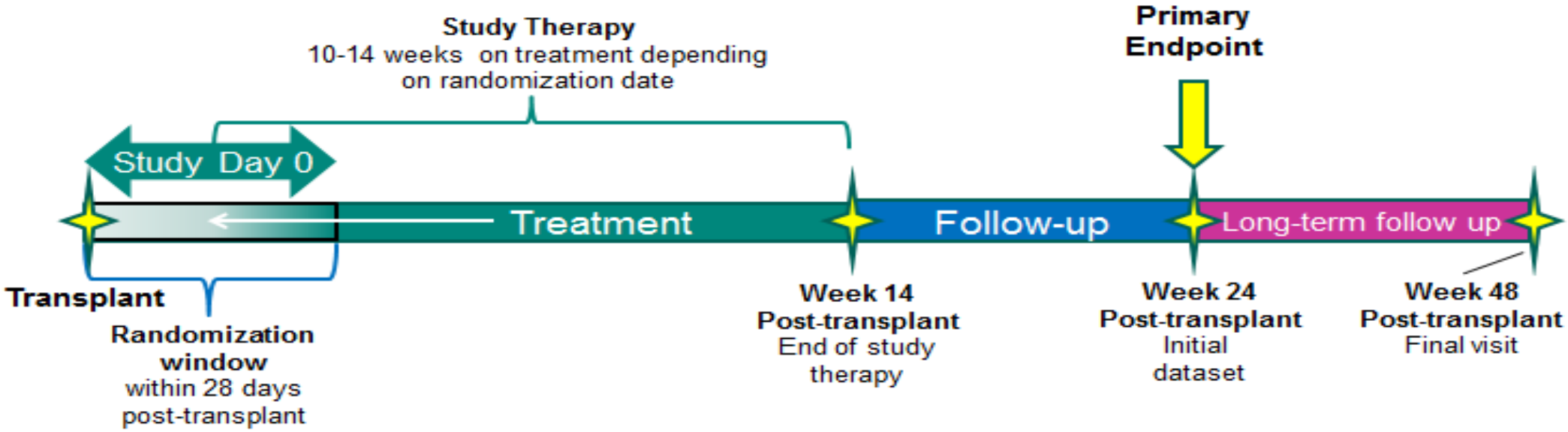
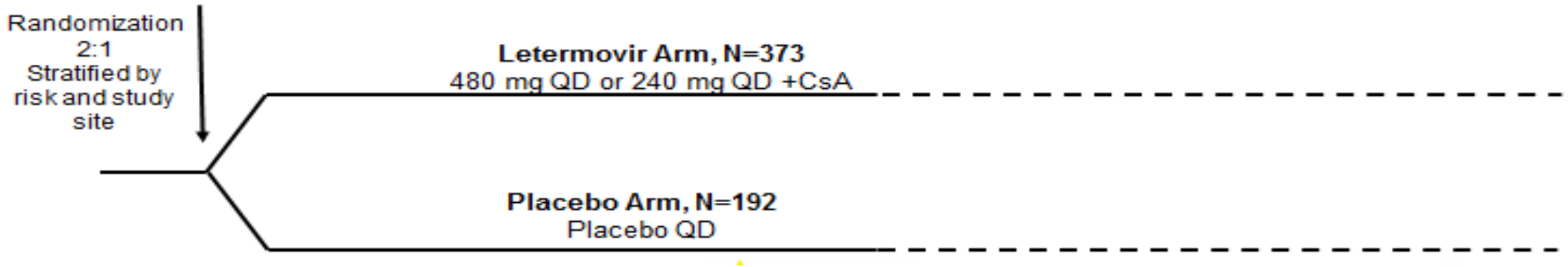
P001: Pivotal Phase 3 Trial Assessing CMV Prophylaxis in HSCT Recipients





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P001: Primary Endpoint: Proportion of Subjects Who Failed Prophylaxis, (NC=F Approach, FAS Population)

Proportion of subjects who failed prophylaxis through Week 24 post-transplant was significantly lower in the letermovir group

	Letermovir (N=325) n (%)	Placebo (N=170) n (%)
Proportion of subjects who failed prophylaxis (primary endpoint)	**122 (37.5)**	**103 (60.6)**
Reasons for failure †		
Clinically significant CMV infection by Week 24	57 (17.5)	71 (41.8)
Initiation of PET based on documented viremia	52 (16.0)	68 (40.0)
CMV end-organ disease	5 (1.5)	3 (1.8)
Discontinued from study before Week 24	56 (17.2)	27 (15.9)
Missing outcome in Week 24 visit window	9 (2.8)	5 (2.9)
Stratum-adjusted treatment difference (Letermovir-Placebo)		
Difference (95% CI)	**-23.5 (-32.5, -14.6)**	
p-value	**<0.0001**	

† The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

NC=F, Non-Completer = Failure

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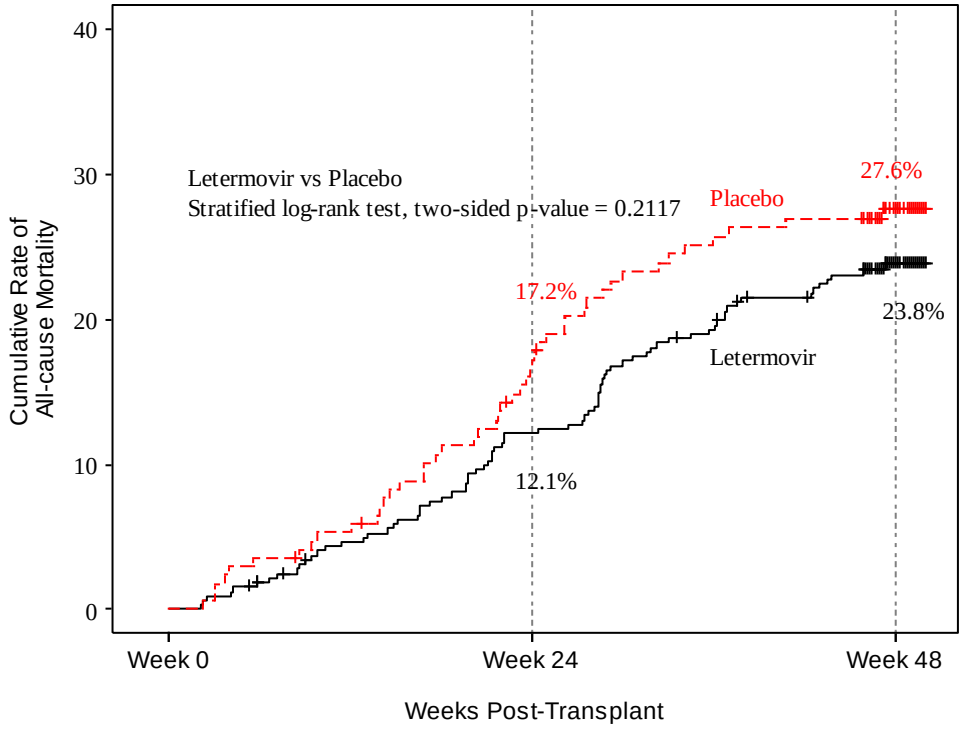
P001: All-cause Mortality Through Week 48 Post-Transplant (FAS)

Data at Week 48 post-transplant shows substantial difference in all-cause mortality between letermovir and placebo



Number of Subjects at Risk			
Letermovir	325	282	165
Placebo	170	139	81

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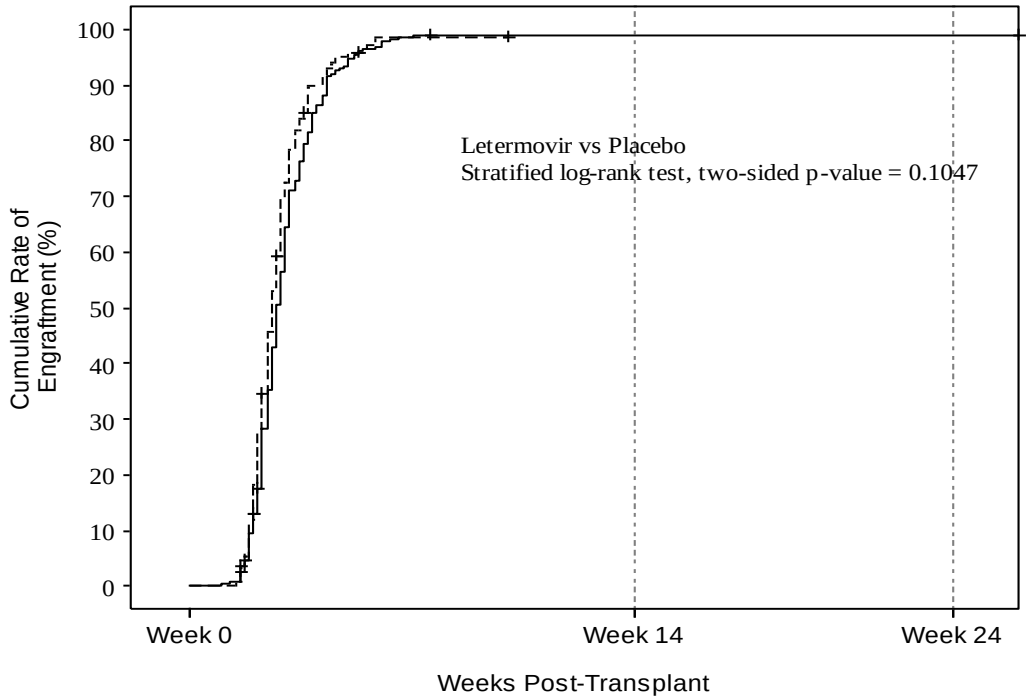
P001:
Hematological Analyses

No evidence of myelotoxicity

- Hematological laboratory parameters similar between letermovir and placebo
- More than 60% of subjects had not engrafted at baseline:
  - Incidence of engraftment similar between letermovir (95%) & placebo (91%)
  - Median time to engraftment similar between letermovir (19 days) & placebo (18 days)



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Ongoing activities

- Application under review (US and EU)
- Prophylaxis study in renal transplant patients
- Pediatric study

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THANK YOU

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