LETTER TO THE EDITOR

A phase II randomized, placebo-controlled, multicenter trial to evaluate the efficacy of cytomegalovirus PepVax vaccine in preventing cytomegalovirus reactivation and disease after allogeneic hematopoietic stem cell transplant

Authors

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A phase 2 randomized, placebo-controlled, multicenter trial to evaluate the efficacy of cytomegalovirus PepVax vaccine in preventing cytomegalovirus reactivation and disease after allogeneic hematopoietic stem cell transplant

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Supplementary data

Supplementary Figure legends

Figure 1S: Enrollment and randomization of HCT recipients. The flow diagram shows the trial profile including enrollment, intervention allocation, follow-up, and data analysis. *Denotes day of primary efficacy endpoint; HCT = hematopoietic stem cell transplant; COH = City of Hope; UMN = University of Minnesota; FHCC = Fred Hutchinson Cancer Center; OSUMC = The Ohio State University Wexner Medical Center; GVHD graft-versus-host disease; AE = adverse event.

Figure 2S: Time-to-event curves for CMV events. Kaplan–Meier estimates are shown, with censoring times indicated. The analysis was conducted by comparing cumulative incidence of CMV event rate by day 100 between PepVax and placebo arm, using Gray's test for competing-risk events. (**A**) Bar indicates the cumulative incidence of CMV events at day 100 post-HCT (primary efficacy endpoint). (**B**) CMV events according to the treatment assignment, in the subgroup of HCT recipients who received a transplant from a CMV seropositive donor (left plot) and that one of HCT recipients who received a transplant from CMV seronegative donor (right plot).

Figure 3S: Frequency of pp65$_{495–503}$-specific CD8 T-cells by HCT donor CMV serostatus. Longitudinal levels (T cells/µl) of pp65$_{495–503}$-specific CD3$^+$ CD8$^+$ T-cells are shown by HCT donor CMV serostatus. Levels were computed using the loess scatterplot smoother providing the marginal geometric mean concentrations through time for each arm (as specified in the color legend). A 95% confidence band is shown in gray, and individual measurement trajectories are shown for each participant up to 7 days before the protocol-defined cytomegalovirus event. Logarithmic spacing of both scales is used to aid visualization. Distribution of pp65$_{495–503}$ specific CD8 T cells levels were approximately normal after log 10-transformation. Generalized estimating equations models were used to assess the vaccine effect on immunological responses All analyses were performed using SAS version 9.4 (SAS institute). The syringe symbol indicates post-HCT day of injections. D$^+$ = HCT CMV seropositive donor; D$^-$ = HCT CMV seronegative donor.

Figure 1S.

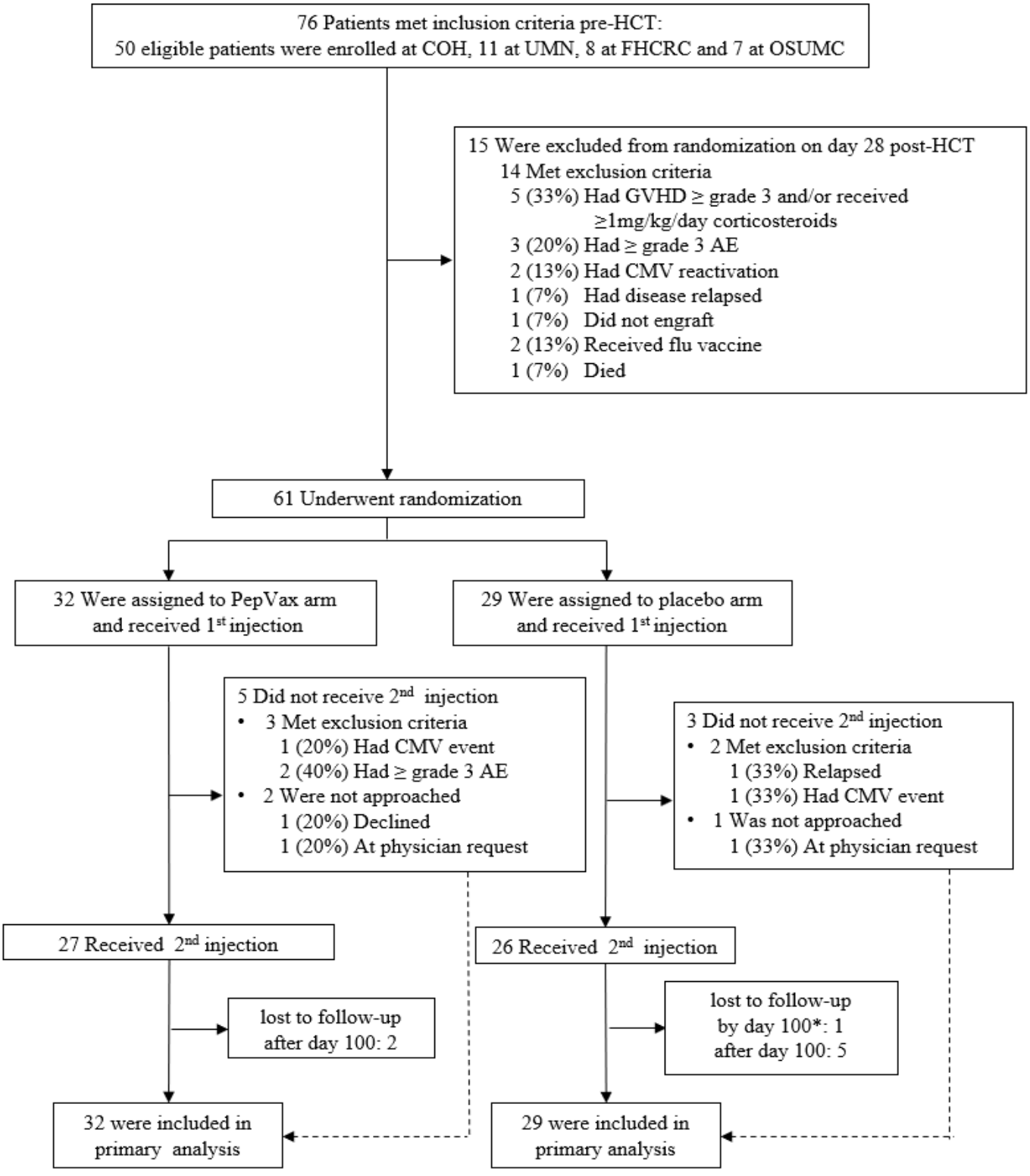
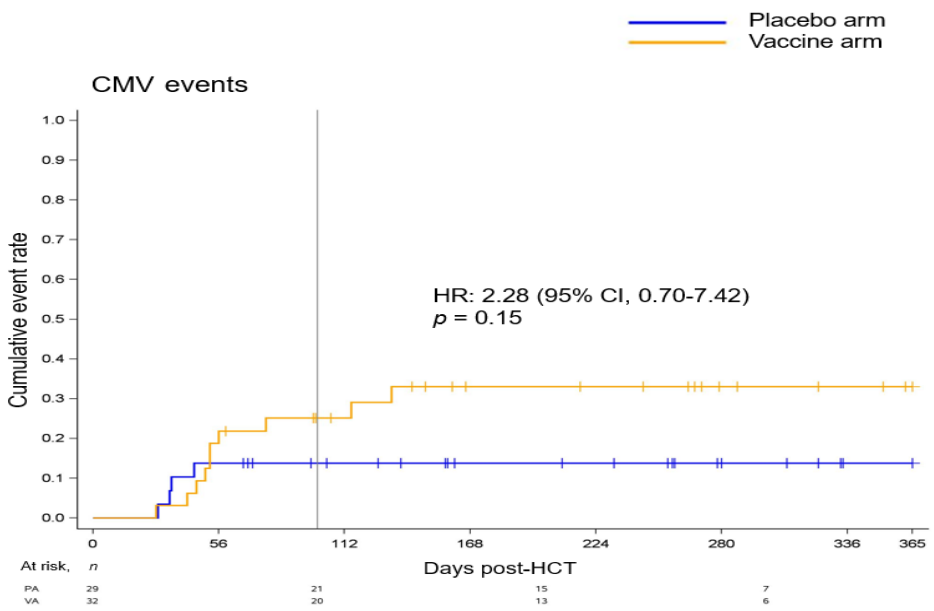

76 Patients met inclusion criteria pre-HCT:
50 eligible patients were enrolled at COH, 11 at UMN, 8 at FHCRC and 7 at OSUMC
15 Were excluded from randomization on day 28 post-HCT
14 Met exclusion criteria
5 (33%) Had GVHD ≥ grade 3 and/or received ≥1mg/kg/day corticosteroids
3 (20%) Had ≥ grade 3 AE
2 (13%) Had CMV reactivation
1 (7%) Had disease relapsed
1 (7%) Did not engraft
2 (13%) Received flu vaccine
1 (7%) Died
61 Underwent randomization
32 Were assigned to PepVax arm and received 1st injection
29 Were assigned to placebo arm and received 1st injection
5 Did not receive 2nd injection
• 3 Met exclusion criteria
1 (20%) Had CMV event
2 (40%) Had ≥ grade 3 AE
• 2 Were not approached
1 (20%) Declined
1 (20%) At physician request
3 Did not receive 2nd injection
• 2 Met exclusion criteria
1 (33%) Relapsed
1 (33%) Had CMV event
• 1 Was not approached
1 (33%) At physician request
27 Received 2nd injection
26 Received 2nd injection
lost to follow-up after day 100: 2
lost to follow-up by day 100*: 1
after day 100: 5
32 were included in primary analysis
29 were included in primary analysis

Figure 2S.

A


Placebo arm
Vaccine arm
CMV events
Cumulative event rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
HR: 2.28 (95% CI, 0.70-7.42)
p = 0.15
0
56
112
168
224
280
336
365
Days post-HCT
At risk, n
PA 29 21 15 7
VA 32 20 13 6

B

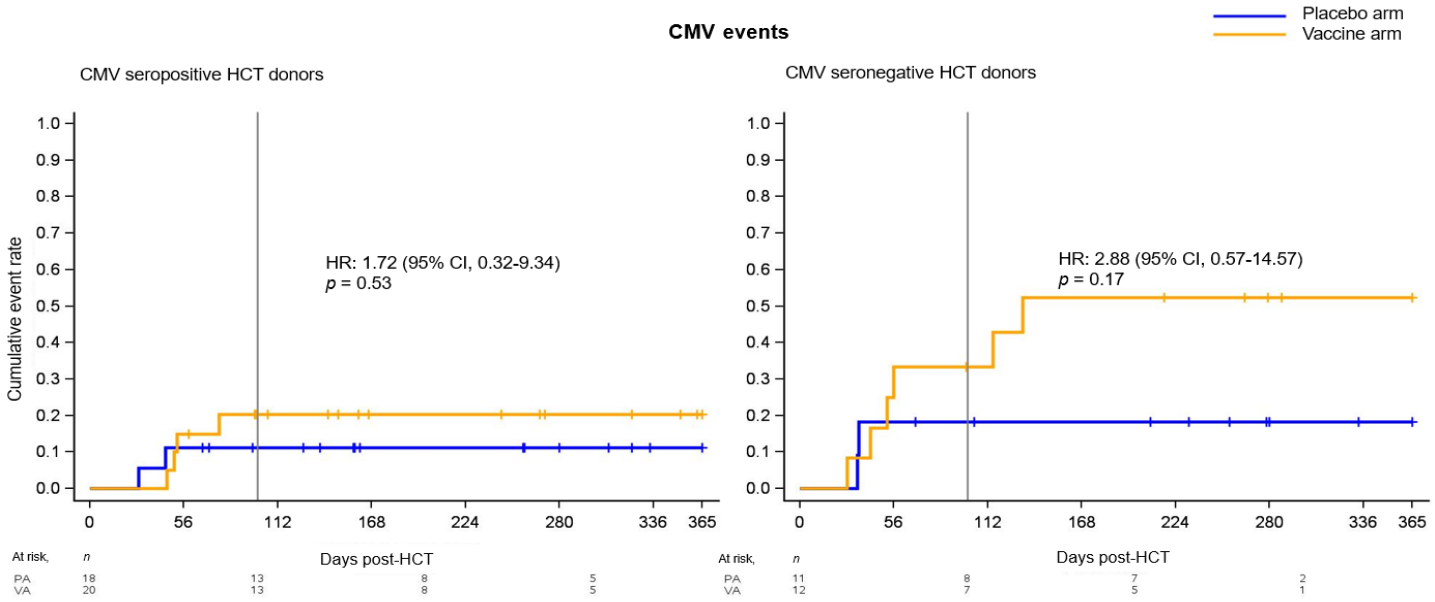
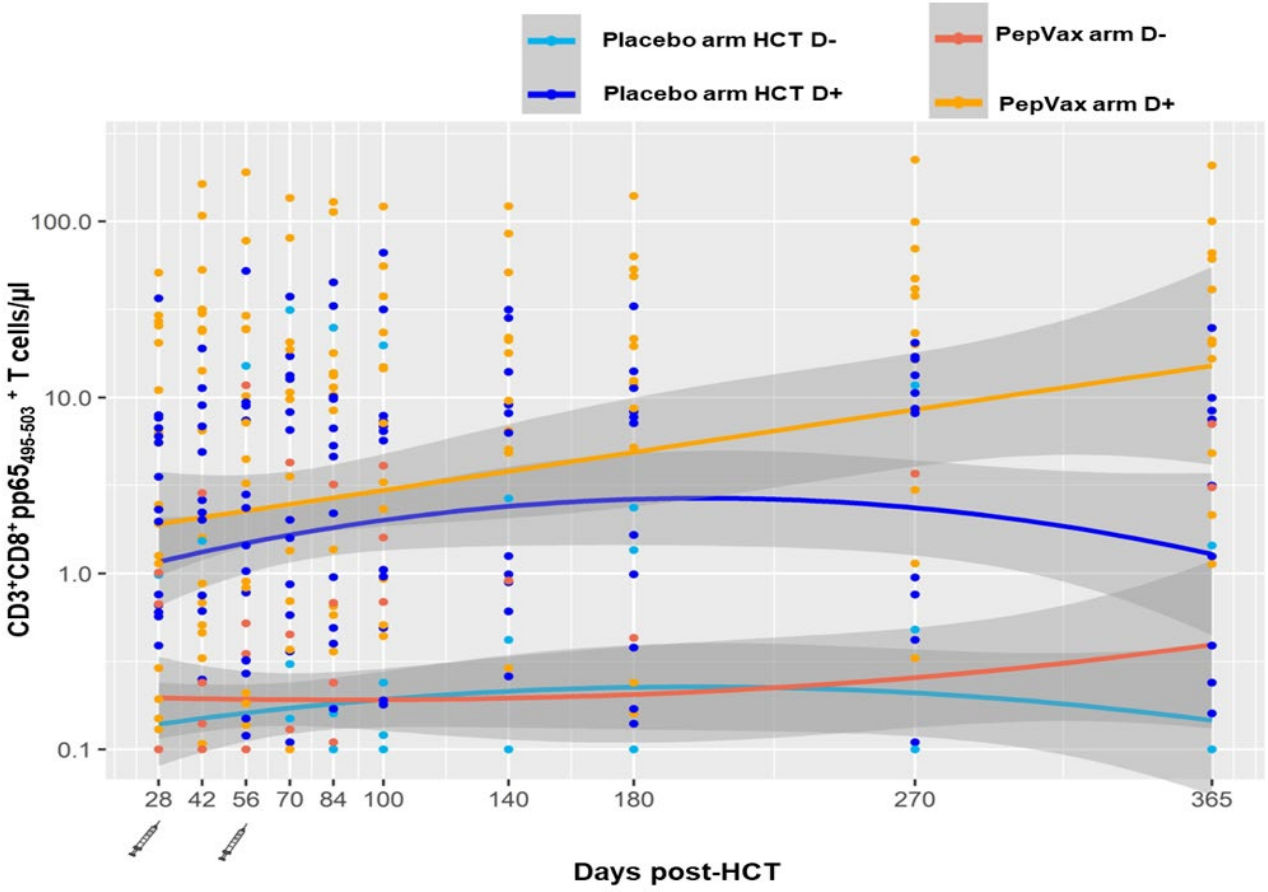
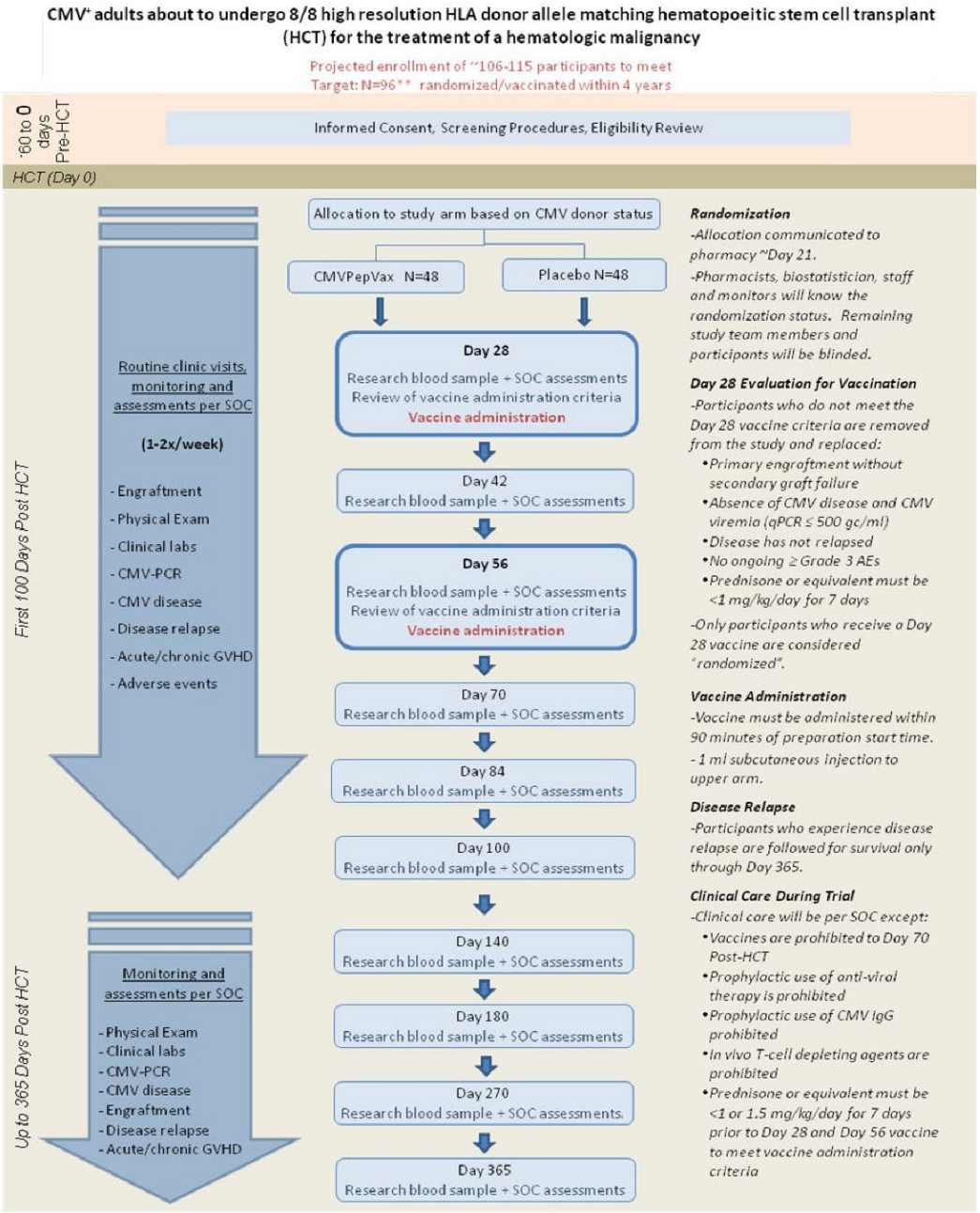

CMV events
Placebo arm
Vaccine arm
CMV seropositive HCT donors
CMV seronegative HCT donors
Cumulative event rate
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
HR: 1.72 (95% CI, 0.32-9.34)
p = 0.53
HR: 2.88 (95% CI, 0.57-14.57)
p = 0.17
0
56
112
168
224
280
336
365
Days post-HCT
At risk, n
PA 18 13 8 5
VA 20 13 8 5
At risk, n
PA 11 8 7 2
VA 12 7 5 1

Figure 3S.


Placebo arm HCT D-
Placebo arm HCT D+
PepVax arm D-
PepVax arm D+
100.0
10.0
1.0
0.1
CD3+CD8+pp65495-503+ T cells/µl
28
42
56
70
84
100
140
180
270
365
Days post-HCT

Protocol experimental design schema



**Interim analysis for futility when 48 participants reach Day 100:study will continue if CMV reactivation is greater in the Placebo arm vs. the CMVPepVax arm

**Safety review for severe acute GVHD and non-relapse mortality will occur as the 12th, 24th, and 36th participant on the CMVPepVax arm reach Day 100