Efficacy and Safety of an Adjuvanted Herpes Zoster Subunit Vaccine in Autologous Hematopoietic Stem Cell Transplant Recipients 18 Years of Age or Older

First Results of the Phase 3 Randomized, Placebo-Controlled ZOE-HSCT Clinical Trial

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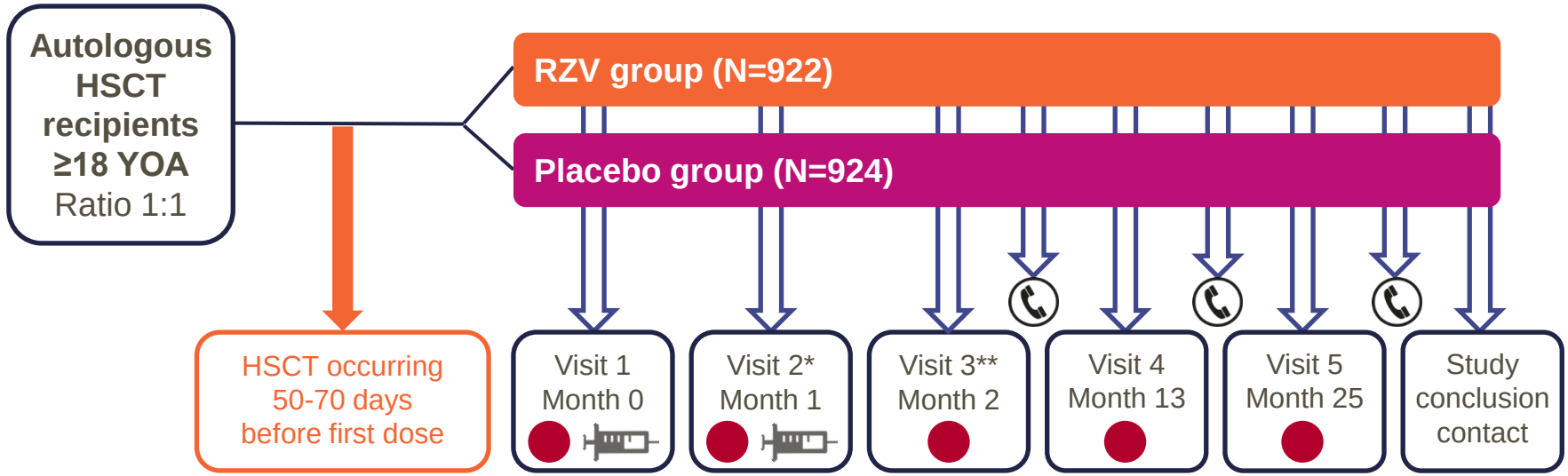
Introduction

- Herpes zoster (HZ) reactivation is frequent after hematopoietic stem cell transplantation (HSCT)[1,2] and associated with diminished T-cell immunity.[3]
- Safe prevention is fundamental and recombinant subunit vaccines could be used as an alternative to prolonged acyclovir prophylaxis.
- The Recombinant Zoster Vaccine (RZV) containing varicella zoster virus (VZV) glycoprotein E (gE) and the $AS01_B$ Adjuvant System showed >90% vaccine efficacy (VE) in immunocompetent adults ≥50 years of age (YOA).[4]
- RZV is licensed in Canada, US, Europe, Australia, and Japan in adults ≥50 YOA.[5,6]
- National Advisory Committee on Immunization strongly recommends RZV in immunocompetent adults ≥50 YOA without contraindications[7]
- In a phase 1/2a study, 2 doses of RZV elicited robust immune responses in autologous HSCT recipients and had a clinically acceptable safety profile.[8]
- Here, we report VE against HZ, postherpetic neuralgia (PHN), other HZ complications and HZ-related hospitalizations, as well as safety results when RZV is administered after autologous HSCT.

1. Berman et al, Bone Marrow Transplant 2006;37:73–80; 2. Rogers et al, Transpl Infect Dis 2011;13:480–4; 3. Hata et al, N Engl J Med 2002;347:26–34; 4. Lal et al, N Engl J Med 2015;372:2087–96; 5. https://www.gsk.com/en-gb/media/press-releases/shingrix-approved-in-europe-and-japan-for-the-prevention-of-shingles-in-adults-aged-50-and-over/. 6. https://www.tga.gov.au/prescription-medicines-registration-new-chemical-entities-Australia. 7. Public Health Agency of Canada. Updated Recommendations on the use of Herpes Zoster Vaccines. June 2018. https://www.canada.ca/en/services/health/publications/healthy-living/updated-recommendations-use-herpes-zoster-vaccines.html 8. Stadtmauer et al, Blood 2014;124:2921–9.

Zoster-002: Study design

Phase III, randomized, multicenter, observer-blind, placebo-controlled



***** Second dose was administered 1 to 2 months after the first dose.
****** Visit 3: approximately one month after the second vaccination
Blood sampling collected from all subjects at Visit 1 & Visit 3. Additional blood samples collected from sub-cohorts at all visits

HSCT: haematopoietic stem cell transplant; **YOA:** years of age; **RZV:** recombinant zoster vaccine; **N:** number of participants in the total vaccinated cohort.
de la Serna, et al. ASBMT, Utah. Feb, 21-25, 2018. Abstract available at https://bmt.confex.com/tandem/2018/meetingapp.cgi/Paper/11724

Zoster-002: Study objectives

Clinical Trial Registration: NCT01610414

Primary objective

– To evaluate VE in the prevention of HZ in autologous HSCT recipients 18 years of age and older.
  – *Clinically meaningful overall HZ VE demonstrated if the lower limit (LL) of the 95% confidence interval (CI) is above 0%.*

Secondary objectives

– To evaluate VE in the reduction of confirmed HZ-associated complications in autologous HSCT recipients 18 years of age and older;

– To evaluate VE in the prevention of PHN in autologous HSCT recipients 18 years of age and older.

– To evaluate vaccine safety and reactogenicity in autologous HSCT recipients 18 years of age and older.

Tertiary objective

- To evaluate VE in the prevention of HZ-associated hospitalizations in autologous HSCT recipients 18 years of age and older.

VE: vaccine efficacy; **HZ:** herpes zoster; **HSCT:** haematopoietic stem cell transplant; **PHN:** post-herpetic neuralgia.
de la Serna, et al. ASBMT, Utah. Feb, 21-25, 2018. Abstract available at https://bmt.confex.com/tandem/2018/meetingapp.cgi/Paper/11724
Clinicaltrials.gov NCT01610414 https://clinicaltrials.gov/ct2/show/study/NCT01610414?term=115523&rank=1

Zoster-002: Summary of demographic characteristics

Modified Total Vaccinated Cohort (mTVC)*

	RZV	Placebo	Total
N	870	851	1721
Mean age at dose 1 (years)	54.8	55.1	55.0
18-49 YOA **≥50 YOA**	213 657	212 639	425 1296
Underlying disease: **Multiple myeloma** **Other diseases†**	 472 398	 465 386	 937 784

- * Includes subjects who received 2 doses. Excludes subjects who developed HZ within one month post dose-2
- † Underlying diseases for which HSCT was performed, excluding multiple myeloma

N: number of participants in the modified TVC; **RZV:** recombinant zoster vaccine; **YOA:** years of age; **HZ:** herpes zoster

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Efficacy results (mTVC, N = 1721)

Autologous haematopoietic stem cell transplant (Zoster-002)

Zoster-002: Vaccine efficacy against HZ

First or only episode of HZ during the whole study - mTVC

Median follow-up time: 21 months

	RZV		Placebo		VE			
	N	n	N	n	%	LL	UL	P-value*
First or only episode of HZ	870	49	851	135	**68.17**	55.56	77.53	<0.0001

Primary objective met:
Clinically meaningful overall HZ VE demonstrated if the LL of the 95% CI is above 0%.

N: number of subjects included in each group
VE: vaccine efficacy (%; Poisson method)
* two sided exact p-value conditional to number of cases

n: number of subjects having at least one confirmed HZ episode
LL, UL: 95% Lower and Upper confidence limits
CI: confidence interval

Zoster-002: Overall HZ-related endpoints

First or only episode of HZ or PHN or hospitalization - mTVC

	RZV		Placebo		VE			
	N	n	N	n	%	LL	UL	P-value*
HZ-related Complications	870	3	851	13	**77.76**	19.05	95.93	0.0175
PHN	870	1	851	9	**89.27**	22.54	99.76	0.0186
HZ-related Hospitalizations	870	2	851	13	**84.70**	32.15	96.55	0.0135

N: number of subjects included in each group
VE: vaccine efficacy (%; Poisson method)
PHN: post-herpetic neuralgia
* two sided exact p-value conditional to number of cases

n: number of subjects having at least one HZ-related complication or PHN or hospitalization
LL, UL: 95% Lower and Upper confidence limits
mTVC: modified total vaccinated cohort

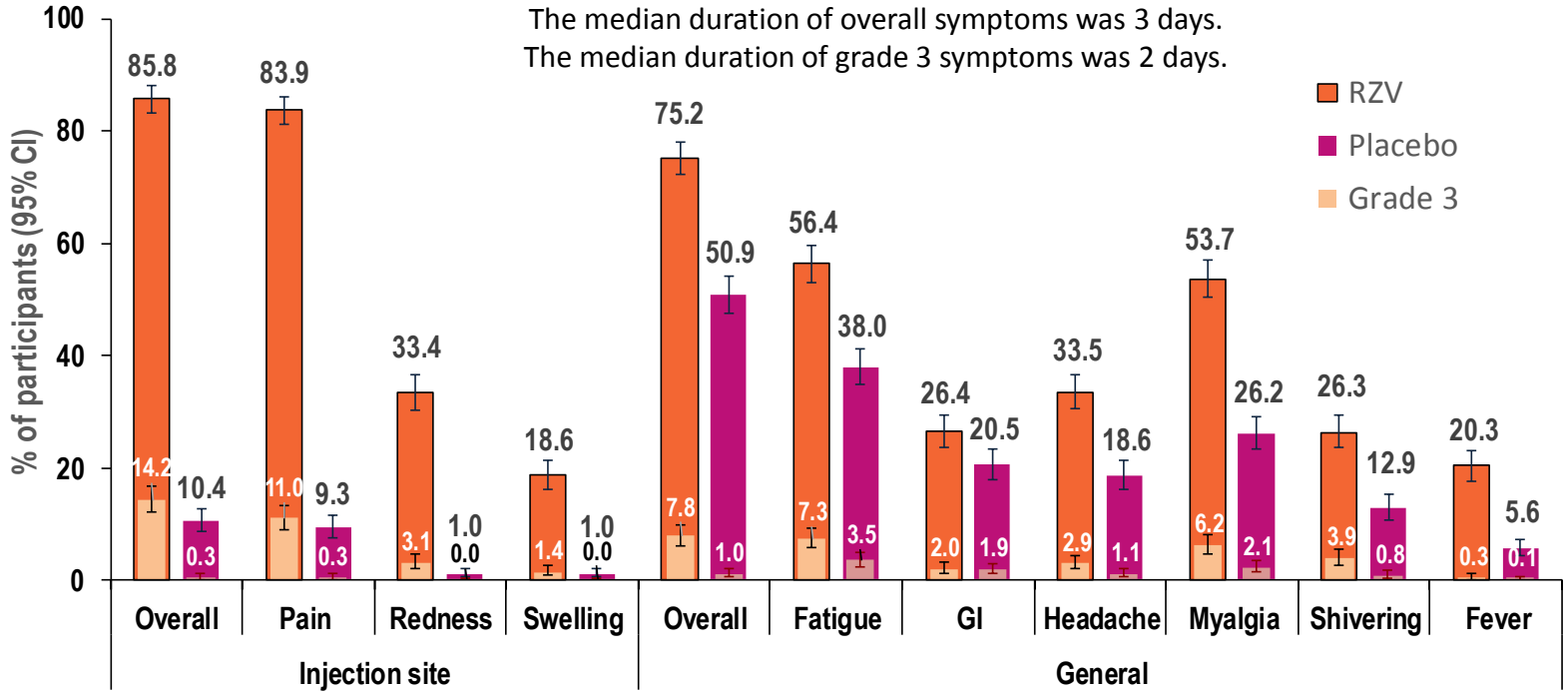
de la Serna, et al. ASBMT, Utah. Feb, 21-25, 2018. Abstract available at https://bmt.confex.com/tandem/2018/meetingapp.cgi/Paper/11724

Safety & Reactogenicity (TVC, N = 1846)

Autologous haematopoietic stem cell transplant (Zoster-002)

Reactogenicity (TVC)

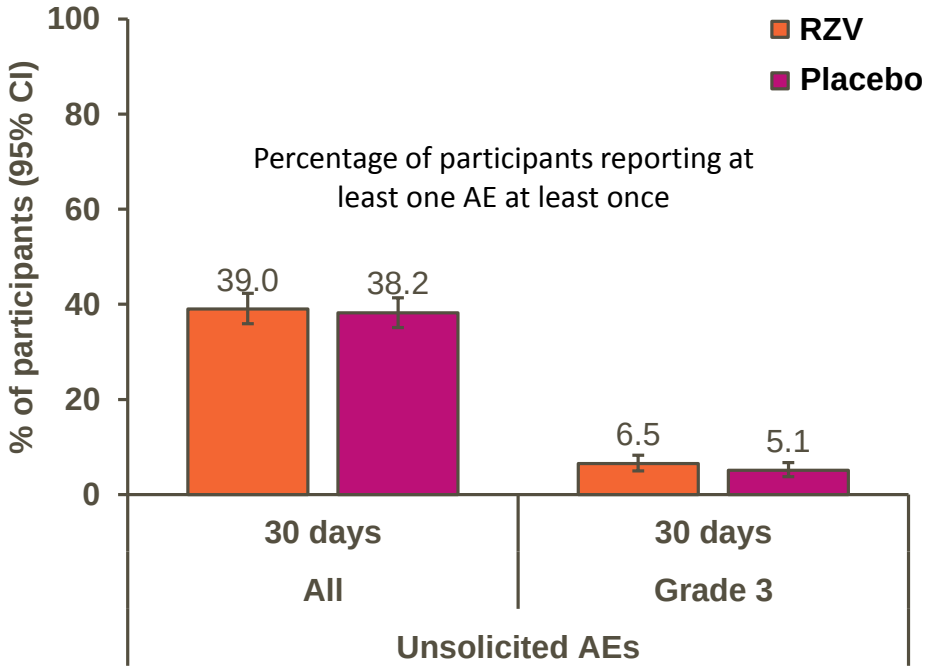
Solicited local and general symptoms were collected up to 7 days after each dose



CI: confidence interval; **GI:** gastrointestinal symptoms (nausea, vomiting, diarrhea and/or abdominal pain); **Fever:** temperature ≥37.5°C (99.5°F) by oral, axillary or tympanic route, or ≥38.0°C (100.4°F) by rectal route; **Grade 3:** severe symptom (for pain: significant pain at rest; prevents normal every day activities; for redness and swelling: diameter >100 mm; for fever: oral temperature ≥39.0°C [102.2°F]; for all others: prevents normal activity). **Error bars** represent 95% CI.

Unsolicited adverse events (TVC)

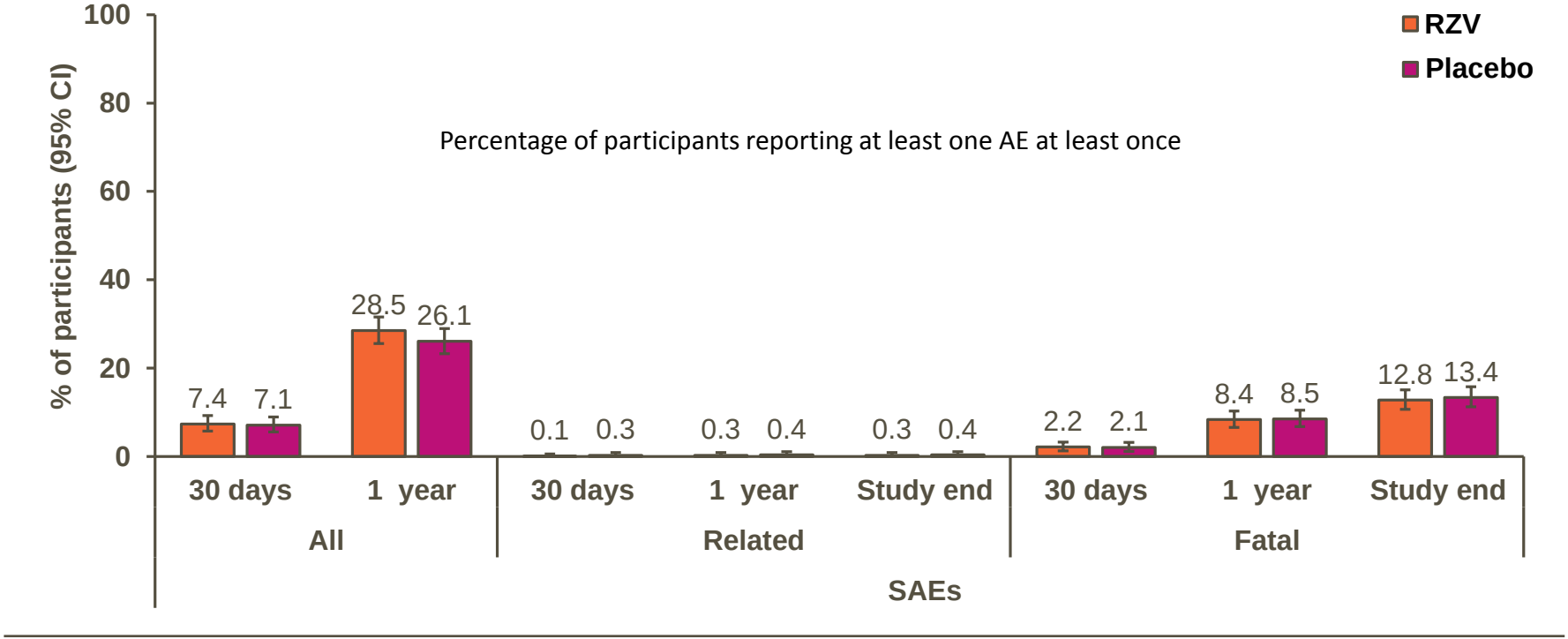
Unsolicited adverse events (AEs) were collected up to 30 days after each dose



CI: confidence interval; **30 days:** up to 30 days after dose 2; **Error bars** represent 95% CI.

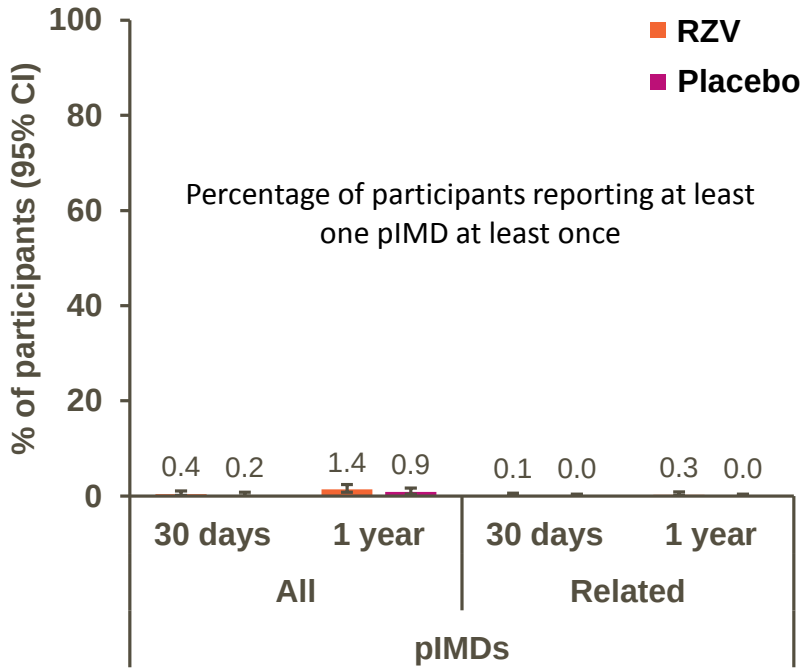
Serious Adverse Events (TVC)

For all participants in the TVC the median safety follow-up time was approximately 29 months.



SAE: serious adverse events; **Related:** considered related to vaccination as per investigator assessment; **30 days:** up to 30 days after dose 2; **1 year:** up to 1 year after dose 2; **CI:** confidence interval; **Error bars** represent 95% CI.

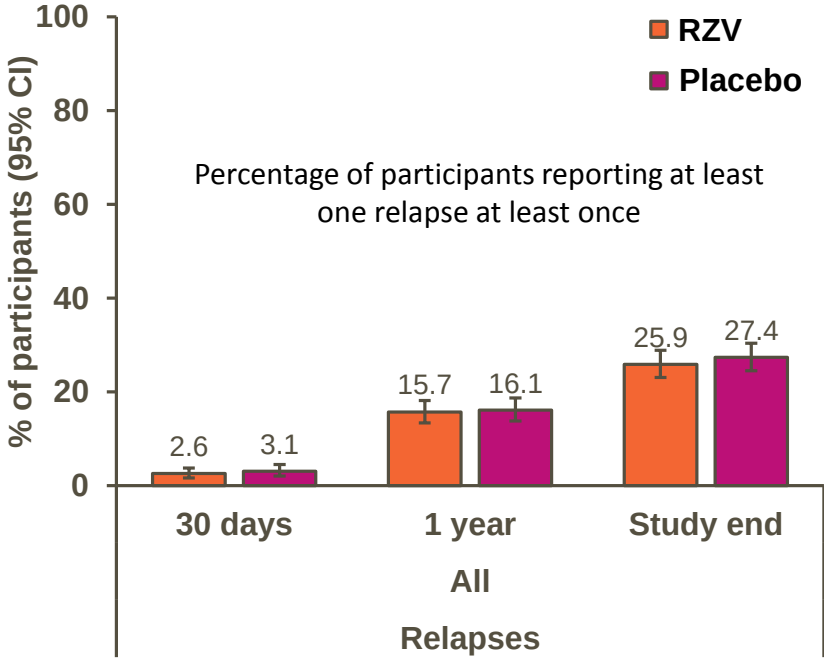
Potential immune-mediated diseases (TVC)



pIMD: potential immune-mediated disease; **Related:** considered related to vaccination as per investigator assessment; **30 days:** up to 30 days after dose 2; **1 year:** up to 1 year after dose 2; **CI:** exact confidence interval; **Error bars** represent 95% CI.

Relapse of underlying condition (TVC)

For all participants in the TVC the median safety follow-up time was approximately 29 months.



Relapse: malignancy relapse; **30 days:** up to 30 days after dose 2; **1 year:** up to 1 year after dose 2; **CI:** exact confidence interval; **Error bars** represent 95% CI.

Zoster-002 Conclusions

Autologous hematopoietic stem cell transplant

- The primary objective of the study was met: vaccine efficacy against herpes zoster was 68.17% (95% CI 55.56-77.53)

- Local and systemic reactogenicity were higher in the RZV versus placebo group in line with the observations in previous studies[1-4]

- Overall, the proportion of SAEs, fatal SAEs, pIMDs and relapses were similar between RZV and placebo groups

CI: confidence interval; **pIMD:** potential immune-mediated disease; **SAE:** serious adverse event

de la Serna, et al. ASBMT, Utah. Feb, 21-25, 2018. Abstract available at https://bmt.confex.com/tandem/2018/meetingapp.cgi/Paper/11724 ; 1. Berkowitz EM, et al. J.Infect.Dis. 2015; 211(8): 1279-1287. 2. Stadtmauer EA, et al. Blood, 2014; 124: 2921-2929. 3. Lal H.et al NEJM 2015; 372(12) 2087-2096; 4. Cunningham A. et al. NEJM 2016; 375(11) 1019-1032.

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P. Chandrasekar has nothing to disclose.

Thank You.