Safety, Tolerability, and Efficacy of Inactivated VZV Vaccine (ZV_{IN}) in Recipients of Autologous Hematopoietic Stem Cell Transplant (Auto-HSCT), a Phase 3 Trial

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INTRODUCTION

- Auto-HSCT recipients have increased risk for herpes zoster (HZ) associated with impaired cellular immunity
  - 16%-25% incidence in earlier studies[1]
- Current guidelines recommend antiviral prophylaxis for prevention of HZ after auto-HSCT[2-6]
- In the current era of acyclovir or valacyclovir prophylaxis, 21% of auto-HSCT recipients still develop HZ, usually after prophylaxis is stopped[3,7]
- Live attenuated varicella zoster virus (VZV) Oka strain vaccine (ZOSTAVAX®, Merck and Co.) is approved for prevention of HZ, but generally contraindicated in immunocompromised subjects
- Proof-of-concept studies showed that heat-inactivated VZV vaccine given in multiple doses after auto-HSCT enhances cellular immunity to VZV and reduces risk of HZ[8,9]
- A study of similar heat-inactivated VZV vaccine (ZV_{IN}) in auto-HSCT recipients demonstrated safety and immunogenicity, with significant rises in VZV T-cell and antibody responses[10]

OBJECTIVE

- Evaluate the efficacy and safety of VZV vaccine inactivated by gamma-irradiation (ZV_{IN}) for prevention of HZ and HZ-related complications after auto-HSCT in a phase 3 randomized, double-blind, placebo-controlled multicenter study

METHODS

Key Study Entry Criteria

- ≥18 years of age
- Auto-HSCT for malignancy or any other indication
- History of varicella infection and/or seropositive for VZV antibody
- No malignancy other than Hodgkin's lymphoma with more than 2 disease relapses
- No planned tandem transplants
- No previous VZV vaccine
- No HZ infection within previous year
- No intended antiviral prophylaxis for >6 months after auto-HSCT (antiviral prophylaxis for <6 months allowed)

Study Design

- Eligible subjects were randomly assigned to receive either ZV_{IN} from a consistency lot, ZV_{IN} from a high-antigen lot, or placebo given in a 4-dose regimen
- Randomization stratified by age (<50 years vs ≥50 years) and by intended duration of post-transplant antiviral prophylaxis (≤3 months vs >3 to 6 months)
- Dose 1 of ZV_{IN} or placebo given within 30 days before auto-HSCT; doses 2, 3, and 4 given 30, 60, and 90 days after auto-HSCT
- Subjects followed for duration of study for serious adverse events (AEs) and HZ, confirmed by polymerase chain reaction (PCR) and/or adjudicated by blinded committee

Primary Endpoints

- Primary efficacy endpoint: Incidence of confirmed HZ among subjects receiving consistency lot ZV_{IN} compared with placebo recipients
  - Subjects receiving high-antigen lot ZV_{IN} excluded from efficacy analysis, and data used only for analysis of safety
  - Prespecified criterion for vaccine efficacy (VE_{HZ}): The lower bound of the 95% confidence interval (CI) was >25% for relative reduction of hazard ratio (HR) of HZ in ZV_{IN} subjects compared with placebo recipients
- Primary safety endpoint: Incidence of serious AEs up to 28 days after 4th vaccination dose

Secondary Endpoints

- Prevention of moderate-to-severe HZ-associated pain
  - Moderate-to-severe HZ-associated pain was defined as ≥2 occurrences of a score of ≥3 (0 to 10 point scale) on the Zoster Brief Pain Inventory (ZBPI) at any time from onset of HZ through the end of the 6-month HZ follow-up period
- Prevention of post-herpetic neuralgia (PHN) beyond 90 days after onset of HZ
  - PHN defined as pain in the area of the HZ rash with a "worst pain in the last 24 hours" score of ≥3 on the ZBPI that persists or recurs beyond 90 days after onset of HZ rash
- Prevention of HZ-associated complications, adjudicated by blinded committee, including:
  - Hospitalization or prolongation of hospitalization due to HZ
  - Disseminated HZ (including disseminated HZ rash or VZV viremia)
  - Visceral HZ
  - Ophthalmic HZ
  - Neurological impairment due to HZ
  - Administration of intravenous acyclovir therapy for treatment of HZ post-auto-HSCT

RESULTS

Table 1. Subject Baseline Characteristics

Characteristic	ZV_{IN} Consistency Lot	ZV_{IN} High-Antigen Lot	Placebo
No. of subjects	**560**	**106**	**564**
Median age, y (range)	57 (19-76)	56 (21-75)	56 (19-79)
Sex, n (%)			
Male	357 (64)	58 (55)	360 (64)
Female	203 (36)	48 (45)	204 (36)
Underlying disease, n (%)			
Non-Hodgkin's lymphoma	234 (42)	42 (40)	250 (44)
Hodgkin's disease	56 (10)	10 (9)	53 (9)
Multiple myeloma	244 (44)	50 (47)	229 (41)
Acute leukemia	12 (2)	1 (1)	11 (2)
Others	14 (2)	3 (3)	21 (4)
Conditioning regimen, n (%)			
Chemotherapy	496 (89)	94 (89)	499 (89)
Intended duration of post auto-HSCT prophylaxis, n (%)			
≤3 months	239 (43)	43 (41)	255 (45)
>3 to 6 months	320 (57)	63 (59)	308 (55)
Not reported	1 (0)	0 (0)	1 (0)

Table 2. Post-Auto-HSCT Characteristics

Characteristic	ZV_{IN} Consistency Lot	ZV_{IN} High-Antigen Lot	Placebo
No. of subjects	**538**	**99**	**535**
Post auto-HSCT maintenance therapy, n (%)			
Yes	196 (36)	37 (37)	202 (38)
Type of post auto-HSCT maintenance therapy, n (%)			
Rituximab	40 (7)	9 (9)	41 (8)
Brentuximab	12 (2)	1 (1)	7 (1)
Lenalidomide	83 (15)	13 (13)	83 (16)
Bortezomib	61 (11)	14 (14)	71 (13)
Post auto-HSCT relapse, n (%)			
Yes	160 (30)	32 (32)	175 (33)
Duration of post auto-HSCT antiviral agents, n (%)			
≤3 months	169 (31)	32 (32)	153 (29)
>3 to 6 months	102 (19)	23 (23)	106 (20)
>6 months	211 (39)	39 (39)	233 (44)
None	56 (10)	5 (5)	43 (8)

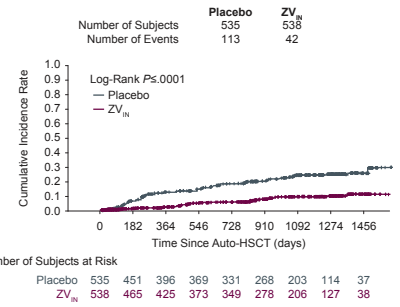
Primary Efficacy Endpoint

Table 3. Incidence of Confirmed HZ Cases

	ZV_{IN} Consistency Lots (N=560)				Placebo (N=564)				
Efficacy Measure	n[a]	m[b]	Total Follow-up Time, Person-Years	Observed Incidence Rate, Per 1000 Person-Years	n[a]	m[b]	Total Follow-up Time, Person-Years	Observed Incidence Rate, Per 1000 Person-Years	Estimated VE_{HZ} Point Estimate (95% CI)[c]
HZ	42	538	1277	32.9	113	535	1230	91.9	0.64 (0.48, 0.75)

[a]n=Number of subjects with confirmed HZ cases.
[b]m=Number of subjects in modified intention-to-treat (MITT) population (1 dose of vaccine and auto-HSCT).
[c]Point estimate and 95% CI of vaccine efficacy obtained from Cox proportional hazards regression model adjusted for age and intended duration of antiviral prophylaxis; vaccine efficacy calculated as 1 minus the HR of HZ in ZV_{IN} vs placebo group.
Prespecified success criterion for VE_{HZ} met (lower bound of 95% CI of 48% was greater than 25%).

Figure 1. Kaplan-Meier Estimate of the Cumulative Incidence of Confirmed HZ Cases



Number of Subjects at Risk

Placebo	535	451	396	369	331	268	203	114	37
ZV_{IN}	538	465	425	373	349	278	206	127	38

Secondary Endpoints

Table 4. Incidences of Moderate-to-Severe HZ Pain, PHN, and HZ Complications

	ZV_{IN} Consistency Lots (N=560)				Placebo (N=564)				
Efficacy Measure	n[a]	m[b]	Total Follow-up Time, Person-Years	Observed Incidence Rate, Per 1000 Person-Years	n[a]	m[b]	Total Follow-up Time, Person-Years	Observed Incidence Rate, Per 1000 Person-Years	Estimated VE_{HZ} Point Estimate (95% CI)[c]
Moderate-to-severe HZ pain	19	538	1277	14.9	61	535	1230	49.6	0.70 (0.49, 0.82)
PHN	3	538	1277	2.3	18	535	1230	14.6	0.84 (0.45, 0.95)
HZ complications	12	538	1277	9.4	44	535	1230	35.8	0.74 (0.45, 0.86)

[a]n=Number of subjects with confirmed secondary endpoints.
[b]m=Number of subjects in MITT population (one dose of vaccine and auto-HSCT).
[c]Point estimate and 95% CI of vaccine efficacy obtained from Cox proportional hazards regression model adjusted for age and intended duration of antiviral prophylaxis. Vaccine efficacy calculated as 1 minus the HR of endpoint in ZV_{IN} vs placebo group.

Table 5. Incidences of Confirmed Cases of HZ by Age Stratum and Antiviral Prophylaxis Stratum

	ZV_{IN} Consistency Lots (N=560)				Placebo (N=564)			
Stratum	n[a]	m[b]	Total Follow-up Time, Person-Years	Observed Incidence Rate, Per 1000 Person-Years (95% CI)	n[a]	m[b]	Total Follow-up Time, Person-Years	Observed Incidence Rate, Per 1000 Person-Years (95% CI)
Subjects <50 years of age	7	154	359	19.5 (7.8, 40.2)	27	151	344	78.5 (51.8, 114.3)
Subjects ≥50 years of age	35	384	918	38.1 (26.5, 40.2)	86	384	886	97.1 (77.6, 119.9)
Subjects with ≤3 months post-transplant antiviral prophylaxis	20	228	546	30.1 (22.4, 56.6)	51	239	530	96.2 (71.6, 126.5)
Subjects with 3-6 months post-transplant antiviral prophylaxis	22	310	731	32.9 (18.9, 45.5)	62	296	700	88.6 (67.9, 113.6)

[a]n=Number of subjects with confirmed HZ cases.
[b]m=Number of subjects in MITT population (one dose of vaccine and auto-HSCT).

Safety Analysis

Table 6. Overall Summary of Adverse Events Up to 28 Days After 4th Vaccination Dose

	ZV_{IN}[a]	Placebo	Risk Differences (95% CI)
No. of subjects	**657**	**554**	
Subjects with ≥1 AE, n (%)	644 (97)	537 (96.9)	0.7% (-1.1, 2.7)
Vaccine-related AE, n (%)	214 (32.6)	70 (12.6)	20.0% (15.5, 24.5)
Injection site AE[b]	191 (29.1)	36 (6.5)	22.6% (18.5, 26.6)
Non-injection site AE	42 (6.4)	38 (6.9)	-0.4% (-3.3, 2.4)
Serious AE, n (%)	216 (32.9)	181 (32.7)	0.2% (-5.1, 5.5)
Serious vaccine-related AE, n (%)	5 (0.8)	5 (0.9)	0.1% (-1.4, 1.1)
Discontinued due to AE, n (%)	20 (3.0)	17 (3.1)	-0.1% (-2.1, 2.0)
Death, n (%)	41 (6.2)	35 (6.3)	-0.1% (-2.9, 2.7)

[a]ZV_{IN} includes subjects receiving consistency lots or high-antigen lot.
[b]Pain, erythema, swelling, or induration at injection site.

Table 7. Most Common Systemic AEs (Incidence >15%) Up to 28 Days After 4th Vaccination Dose[a,b,c]

	ZV_{IN}	Placebo
No. of subjects	**657**	**554**
Each AE, n (%)		
Diarrhea	395 (60.1)	343 (61.9)
Nausea	371 (56.5)	320 (57.8)
Pyrexia	327 (49.8)	260 (46.9)
Mucosal inflammation	261 (39.7)	231 (41.7)
Thrombocytopenia	239 (36.4)	213 (38.4)
Febrile neutropenia	217 (33.9)	157 (28.3)
Vomiting	214 (32.6)	203 (36.6)
Anemia	175 (26.6)	135 (24.4)
Neutropenia	165 (25.1)	139 (23.5)
Decreased appetite	152 (23.1)	132 (23.8)
Fatigue	143 (21.8)	120 (20.7)
Hypokalemia	140 (21.3)	110 (19.9)
Constipation	106 (16.1)	102 (18.4)

[a]Differences not statistically significant.
[b]Every subject is counted a single time for each applicable row and column.
[c]ZV_{IN} includes subjects receiving consistency lots or high-antigen lot.

Table 8. Most Common Serious AEs by Specific Term (>1% Incidence) Up to 28 Days After 4th Vaccination Dose[a,b,c]

	ZV_{IN}	Placebo
No. of subjects	**657**	**554**
Each AE, n (%)		
Febrile neutropenia	35 (5.3)	27 (4.9)
Pyrexia	21 (3.2)	20 (3.6)
Pneumonia	16 (2.4)	17 (3.1)
Sepsis	10 (1.5)	8 (1.4)
Mucosal inflamation	8 (1.2)	5 (0.9)
Plasma cell myeloma	8 (1.2)	5 (0.9)
Diffuse large B-cell lymphoma	6 (0.9)	7 (1.3)
Non-Hodgkin's lymphoma, recurrent	3 (0.5)	7 (1.3)

[a]Differences not statistically significant.
[b]Every subject is counted a single time for each applicable row and column.
[c]ZV_{IN} includes subjects receiving consistency lots or high-antigen lot.

EFFICACY SUMMARY

- Estimated VE_{HZ}=64%
- Estimated VE_{PAIN}=70%
- Estimated VE_{PHN}=84%
- Estimated $VE_{COMPLICATIONS}$=74%

SAFETY SUMMARY

- Among the ZV_{IN} and placebo groups:
  - Higher proportion of injection-site AEs was seen in the ZV_{IN} group
  - Systemic AEs were similar between groups, except:
    - Stomatitis (ZV_{IN}: 12.8%; placebo: 9.0%)
    - Pruritus (ZV_{IN}: 10.0%; placebo: 6.7%)
    - Weight decrease (ZV_{IN}: 3.5%; placebo: 1.4%)
    - Malaise (ZV_{IN}: 2.3%; placebo: 0.7%)
  - Incidences of serious AEs were similar

CONCLUSIONS

- ZV_{IN} is effective for prevention of HZ after auto-HSCT
- ZV_{IN} reduces the incidence of moderate-to-severe HZ pain, PHN, and HZ complications after auto-HSCT
- ZV_{IN} is well tolerated in auto-HSCT recipients

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Disclosures

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- Lei Pang is an employee of Merck and owns Merck stock/options
- Yanli Zhao is an employee of Merck and owns Merck stock/options
- Ivan Chan is a former Merck employee
- Jon Stek is an employee of Merck and owns Merck stock/options
- Susan Kaplan is an employee of Merck and owns Merck stock/options
- Janie Parrino is a former Merck employee and owns Merck stock/options
- Paula Annunziato is an employee of Merck
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http://tinyurl.com/ldv2flo

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