Table 3. HZ-related medication types in patients with confirmed HZ

Medication class	ZOE-50 study						ZOE-70 study						ZOE-HSCT study*					
	RZV (N=9)		Placebo (N=254)		Total (N=263)		RZV (N=23)		Placebo (N=223)		Total (N=246)		RZV (N=49)		Placebo (N=135)		Total (N=184)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Non-opioids†	6	66.7	155	61.0	161	61.2	6	26.1	103	46.2	109	44.3	22	44.9	62	45.9	84	45.7
Weak opioids†	0	0	49	19.3	49	18.6	2	8.7	30	13.5	32	13.0	6	12.2	34	25.2	40	21.7
Strong opioids†	0	0	21	8.3	21	8.0	0	0	5	2.2	5	2.0	5	10.2	12	8.9	17	9.2
Corticosteroids	3	33.3	21	8.3	24	9.1	1	4.3	10	4.5	11	4.5	2	4.1	14	10.4	16	8.7
Antidepressants	0	0	17	6.7	17	6.5	1	4.3	18	8.1	19	7.7	3	6.1	13	9.6	16	8.7
Psychiatric medications	0	0	55	21.7	55	20.9	3	13.0	35	15.7	38	15.4	8	16.3	42	31.1	50	27.2
Anesthetics	0	0	15	5.9	15	5.7	0	0	11	4.9	11	4.5	0	0	7	5.2	7	3.8
Antihistamines	0	0	10	3.9	10	3.8	1	4.3	9	4.0	10	4.1	1	2.0	11	8.1	12	6.5
GI medications	1	11.1	24	9.4	25	9.5	0	0	6	2.7	6	2.4	2	4.1	2	1.5	4	2.2
Antibiotics	1	11.1	37	14.6	38	14.4	2	8.7	32	14.3	34	13.8	5	10.2	14	10.4	19	10.3
Muscle relaxants	0	0	1	0.4	1	0.4	0	0	2	0.9	2	0.8	0	0	0	0	0	0
Other medications	3	33.3	54	21.3	57	21.7	3	13.0	42	18.8	45	18.3	6	12.2	19	14.1	25	13.6

*This analysis excluded pain medication linked to a confirmed HZ case after the start of relapse treatment; **GI**, gastro-intestinal; **HZ**, herpes zoster; **N**, number of patients with at least one confirmed HZ episode; **n (%)**, number (percentage) of patients with at least one event in the specified category; **RZV**, recombinant zoster vaccine.
†Based on the World Health Organization's pain relief ladder (WHO's Pain Relief Ladder, 2019. Available at: www.who.int/cancer/palliative/painladder/en/): non-opioids (e.g. nonsteroidal anti-inflammatory drugs and paracetamol [acetaminophen]), weak opioids (e.g. codeine) and strong opioids (e.g. morphine, oxycodone), each with or without adjuvant therapies (e.g. corticosteroids or psychiatric medication).

Conclusion. In addition to a high VE in preventing HZ in these studies, we also observed an attenuation of HZ-related pain, and thus lower use and duration of pain medication in breakthrough cases after RZV vaccination, thereby potentially improving patient quality of life.

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8. The Adjuvanted Recombinant Zoster Vaccine (RZV) Confers Long-term Protection Against Herpes Zoster: Interim Results of an Extension Study (ZOSTER-049) of Two Clinical Trials (ZOE-50 and ZOE-70)

Céline Boutry, PhD[1]; Andrew Hastie, MD[2]; Meng Shi, MS[2]; Javier Diez-Domingo, MD[3]; Juan Carlos Tinoco, MD[4]; Chong-Jen Yu, MD[5]; Paola Pirrotta, PharmD[6]; George Kalema, PhD[7]; Anne Schuind, MD[8]; [1]Aixial, Bruxelles, Belgium, on behalf of GSK, Bruxelles, Brussels Hoofdstedelijk Gewest, Belgium [2]GSK, Rockville, Maryland, United States, Rockville, Maryland; [3]FISABIO, Valencia, Spain, Valencia, Comunidad Valenciana, Spain; [4]Hospital General de Durango, Durango, Mexico, Durango, Durango, Mexico; [5]National Taiwan University Hospital, Taipei, Taiwan, Taipei, Taipei; [6]GSK, Wavre, Belgium, Wavre, Brabant Wallon, Belgium; [7]Keyrus Biopharma, Waterloo, Belgium, on behalf of GSK, Waterloo, Brabant Wallon, Belgium; [8]GSK, Rockville, Maryland

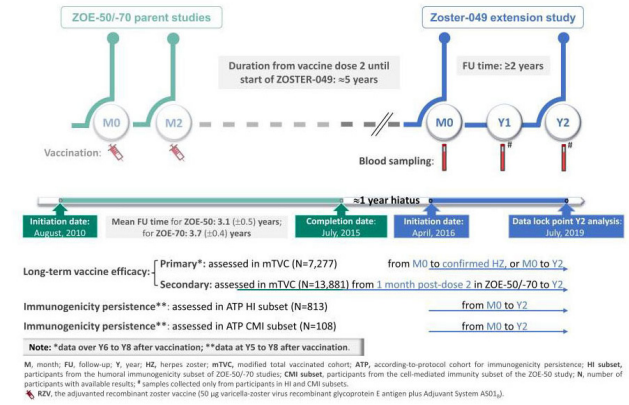
on behalf of the Zoster-049 study group

Session: O-2. Adult Vaccines

Background. Two large-scale phase 3 clinical trials (ZOE-50 [NCT01165177] and ZOE-70 [NCT01165229]) demonstrated that, in adults ≥ 50 years of age followed over a mean period of 3.1 and 3.7 years respectively, the adjuvanted recombinant zoster vaccine (RZV) was efficacious against herpes zoster (HZ), highly immunogenic and had a clinically acceptable safety profile. In this extension study (ZOSTER-049 [NCT02723773]), RZV-induced immunogenicity persistence and long-term vaccine efficacy (VE) against HZ were evaluated; we report interim results after at least 2 years of follow-up (starting and ending ≈5.1 and 7.1 years, respectively, after initial vaccination during the parent studies).

Methods. The study design is detailed in **Figure 1**. Primary objective: VE against HZ over the ZOSTER-049 study. Secondary objectives: VE against HZ from 1 month post-dose 2 in ZOE-50/-70 until the end of observation for year (Y)2 of ZOSTER-049, persistence of vaccine-induced humoral immunogenicity (HI) in terms of anti-gE antibody concentrations (by ELISA) and cell-mediated immune (CMI) response in terms of frequency of gE-specific CD4+ T-cells (by intracellular cytokine staining).

Figure 1. Study design of the extension study in relation to the parent studies. ZOSTER-049 study procedures, timing, endpoints and cohorts



Results. Of the 7,413 participants enrolled in ZOSTER-049, 7,277 were included in the VE analysis (**Figure 2**) and 6,972 reached Y2 of this study. The overall VE against HZ during at least 2 years of follow-up in ZOSTER-049 was 84.0% (95% confidence interval [CI]: 75.9–89.8%). From 1 month post-dose 2 in the ZOE-50/-70 studies until the end of observation for Y2 of ZOSTER-049, the overall VE was 90.9% (95% CI: 88.2–93.2%). Anti-gE antibody concentrations persisted ≈6 times above pre-vaccination levels up to Y8 after vaccination (**Figure 3A**) and the frequency of gE-specific CD4[2+] T-cells remained above baseline from Y6 to Y8 after vaccination (i.e. until the end of observation for Y2 of ZOSTER-049) (**Figure 3B**).

Figure 2. Demographic characteristics of participants included in the ZOSTER-049 study, for the analysis of vaccine efficacy against herpes zoster (mTVC)

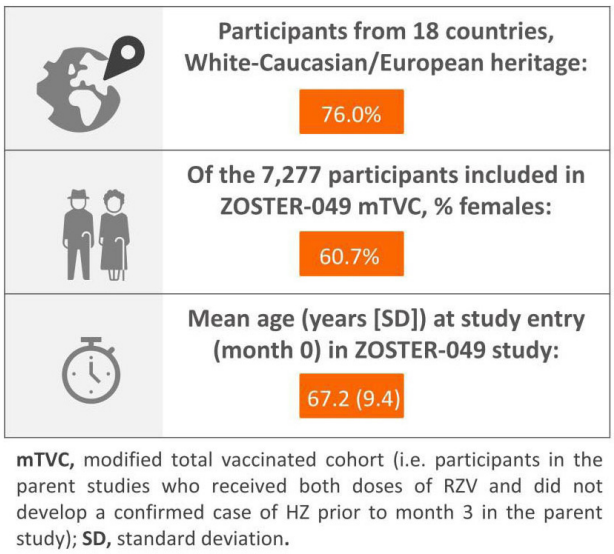
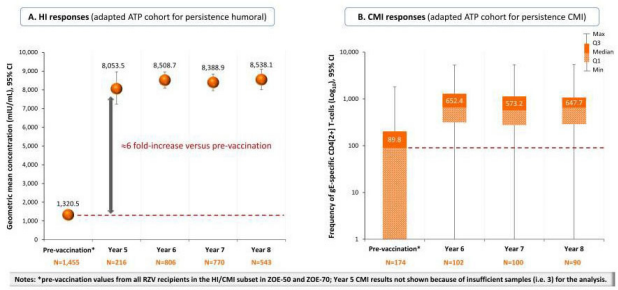


Figure 3. Long-term persistence of humoral immunogenicity (HI) and cell-mediated immune (CMI) responses up to year 8 post-vaccination dose 2 administered in the ZOE-50/-70 studies



Conclusion. RZV demonstrated high VE against HZ until the end of the observation period for this Y2 interim analysis. The HI and CMI responses remained stable and high until the end of observation (i.e. 7.1 years after initial vaccination).

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Disclosures. **Céline Boutry, PhD**, **Aixial** (Consultant) **Andrew Hastie, MD**, **GSK group of companies** (Employee) **Meng Shi, MS**, **GSK group of companies** (Employee) **Javier Diez-Domingo, MD**, **GSK group of companies** (Board Member, Scientific Research Study Investigator, Advisor or Review Panel member)**MSD** (Board Member, Scientific Research Study Investigator, Advisor or Review Panel member) **Paola Pirrotta, PharmD**, **GSK group of companies** (Employee) **George Kalema, PhD**, **GSK group of companies/Keyrus Biopharma** (Consultant) **Anne Schuind, MD**, **GSK** (Employee, Other Financial or Material Support, own GSK stock options or restricted shares as part of renumeration)

9. Evaluation of Synergy Testing Methods for Clinical Labs to Determine Susceptibility of Extensively Drug-resistant Gram-negatives to Ceftazidime/ Avibactam and Aztreonam Combination Therapy

Ayesha Khan, BSC[1]; Samuel G. Erickson, BS[1]; Cedric H. Pettaway, Jr., BS[1]; Cesar A. Arias, M.D., MSc, Ph.D., FIDSA[2]; William R. Miller, MD[3]; Micah M. Bhatti, MD, PhD[4]; [1]McGovern Medical School, Houston, Texas; [2]CARMiG, UTHealth and Center for Infectious Diseases, UTHealth School of Public Health, HOU, TX; Molecular Genetics and Antimicrobial Resistance Unit and International Center for Microbial Genomics, Universidad El Bosque, BOG, COL, Houston, Texas; [3]Center for Antimicrobial Resistance and Microbial Genomics, UTHealth, Houston, Texas; [4]The University of Texas MD Anderson Cancer Center, Houston, Texas

Session: O-3. Advances in Time to Test Results in the Bacteriology Lab

Background. Carbapenem-resistant *Enterobacterales* (CRE) and *Pseudomonas aeruginosa* (CR-PA) producing Metallo-β-lactamases (MBLs) cause severe nosocomial infections with no defined treatment. Combination therapy with ceftazidime/ avibactam (CZA) and aztreonam (ATM) is a potential option, but there is no approved, feasible, synergy testing method for clinical labs to guide clinical decision making. Here, we evaluate the performance of 4 synergy testing methods using gradient-strips or disks.

Methods. We used 10 representative *Enterobacterales* strains, namely, *E. coli, K. pneumoniae,* and *E. cloacea,* and 6 PA strains harboring MBL, GES or non-MBL enzymes (**Fig 1**). 4 strains were successfully treated with CZA-ATM in case reports, the rest were from the CDC AR Bank. Four synergy testing methods were evaluated, *i) Disk stack* (DS), *ii) Disk elution* (DE), *iii) Gradient-strip Stack* (SS), *iv) Gradient-strip Cross* (SX) (**Fig 1**). All methods were run side-by-side as per CLSI guidelines with broth microdilution (BMD) as the reference. Data is the mean of 3 replicates. Synergy is defined as a strain that is resistant (R) to ATM but drops to ≤ the susceptible (S) breakpoint (**Table 1**) in the presence of CZA (**Fig 2**). Categorical agreement (CA), very major error (VME), major error (ME), minor error (MI) were calculated across methods for CZA-ATM synergy relative to BMD.

Summary of synergy testing methods evaluated

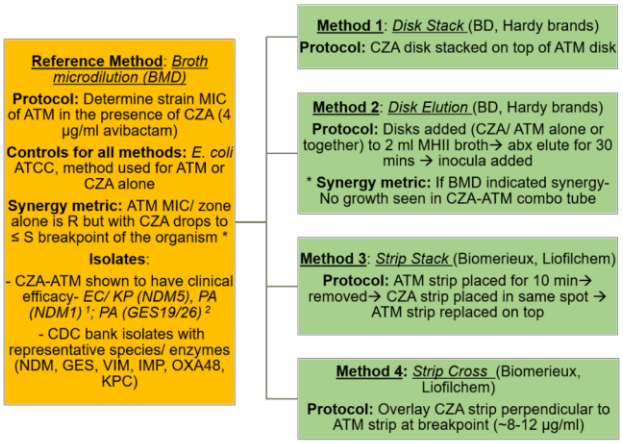

Figure 1. Summary of synergy testing methods evaluated. All methods run simultaneously, results compared to BMD. For all methods except disk elution, MIC or zone diameter is read, synergy is "positive" if strain is resistant (R) to ATM or CZA alone, but susceptible (S) to ATM in presence of CZA (CLSI breakpoints), and "negative" if isolate remains R to ATM-CZA combination. * Disk elution is read for growth or no growth. [1] Khan, A., et. al, 2019, AAC, [2] Khan,A., et. al, 2019 OFID.

CLSI Breakpoints used for this study

Table 1. CLSI Breakpoints used for study.

Species	Antimicrobial	Susceptible	Intermediate	Resistant
Enterobacterales	Aztreonam (MIC ug/ml)	≤ 4	8 ^	≥ 16
	Aztreonam (Disk 30 ug, zone mm)	≥ 21	18-20 ^	≤ 17
	Ceftazidime/ avibactam (MIC ug/ml)	≤ 8	-	≥ 16
	Ceftazidime/ avibactam (Disk 30/20 ug, zone mm)	≥ 21	-	≤ 20
P.aeruginosa	Aztreonam (MIC ug/ml)	≤ 8	16 ^	≥ 32
	Aztreonam (Disk zone mm)	≥ 22	16-21 ^	≤ 15
	Ceftazidime/ avibactam (MIC ug/ml)	≤ 8	-	≥ 16
	Ceftazidime/ avibactam (Disk zone mm)	≥ 21	-	≤ 20

Results. All CRE with NDM and PA with GES were ATM-R, CZA-R and S to the CZA-ATM combination. PA with NDM or VIM remained R to CZA-ATM likely due to other mechanisms of resistance. CA was high for DE (100%), SS (81%, MI 19%), and SX (88%, MI 13%) but low for DS (25%, ME 54%, MI 31%). Representative strains are shown (**Fig 2, Table 2).** Removing PA, CA for DE, SS, and SX was 100% and 20% for DS.

Representative results of strains with each synergy testing method.

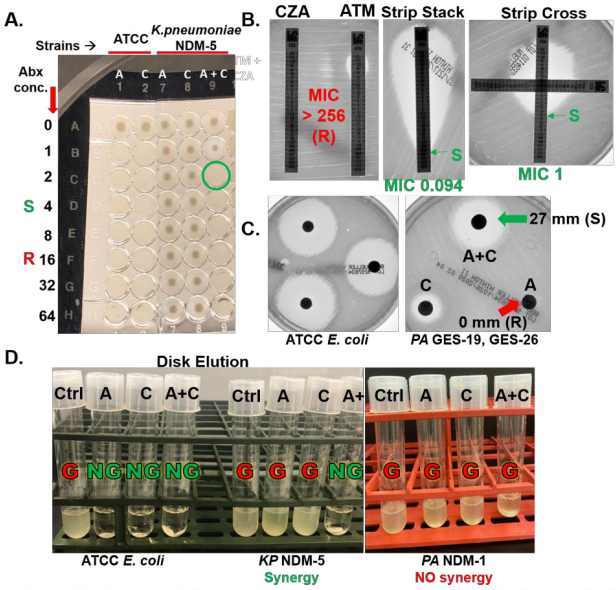

Figure 2. Representative images of synergy testing methods. A. Broth microdilution (BMD) for *K.pneumoniae (KP)* with NDM-1. ATM (A) and CZA (C) MIC >64. ATM MIC with CZA (A+C) at 4 ug/ml avibactam is 2 ug/ml indicating synergy. **B.** Strip methods for ATM resistant (**R**, red) *KP* with ATM susceptibility (**S**, green) restored with CZA present. **C.** Disk stack showing synergy for *P.aeruginosa (PA)* harboring GES-19, GES-26. **D.** Disk elution detects synergy accurately for *KP*, and is precise in detecting the absence of synergy for *PA* with NDM-1 (agreed with BMD). Growth (**G**) and no growth (**NG**) indicated.

Representative data of strains displaying synergy (green) or no synergy (red)

Conclusion. Overall, **DE was the most reliable method for CZA-ATM synergy testing**, and could be a valuable tool in low-resource labs. SS and SX were reliable but prone to technical error. DS had the worst performance. Disks and gradient-strips had identical performance across brands. We propose an algorithm for ATM-R, CZA-R, and MBL-positive CRE, where CZA-ATM synergy testing may be beneficial to guide therapy. These methods are reliable qualitative indicators of the presence or absence of synergy. Synergy testing is not recommended for CR-PA due to complex resistance profiles.