Briefing Document

SHINGRIX*

(Zoster Vaccine Recombinant, Adjuvanted)

Vaccines and Related Biological Products Advisory Committee

Meeting Date: September 13, 2017

*The name ‘SHINGRIX’ has not yet been approved for use by any regulatory authority

EXECUTIVE SUMMARY

SHINGRIX is GSK's candidate Herpes Zoster subunit (HZ/su) vaccine. The proposed indication for HZ/su is: *"HZ/su is a non-live, recombinant vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. By preventing herpes zoster, HZ/su reduces the overall incidence of postherpetic neuralgia."*

Rationale for Vaccine Development

Herpes Zoster (HZ, otherwise known as shingles) is a typically painful and debilitating disease that is caused by the reactivation of latent varicella zoster virus (VZV). Primary VZV infection results in varicella (chickenpox), after which VZV becomes latent in neurons of the dorsal root and cranial nerve ganglia. With increasing age or when the immune system is deficient, VZV-specific immunity wanes and the risk for developing HZ and its most common complication, postherpetic neuralgia (PHN), increases [Cohen, 2013]. Approximately 99% of adults >40 years of age (YOA) in the United States (US) are seropositive for VZV and therefore at risk of developing HZ [Kilgore, 2003; Lebo, 2015]. The available management options for HZ include treatment with antivirals that have a limited impact even with timely initiation. While there are existing drug therapies for the treatment of PHN these have common medication-related adverse effects. Prevention by vaccination therefore offers a health benefit to individuals at risk.

Currently, the only licensed vaccine for the prevention of HZ is *Zostavax*, a live-attenuated vaccine. As demonstrated in phase III studies, *Zostavax* has a vaccine efficacy (VE) against HZ of 69.8% (95% Confidence Interval (CI): 54.1, 80.6) in those 50-59 years of age (YOA), 51% (95% CI: 44, 58) in those ≥60 YOA, 41% (95% CI: 28, 52) in those 70-79 YOA, and 18% (95% CI: <0, 48) in those ≥80 YOA [*Zostavax* Prescribing Information, 2017]. The longer term efficacy and effectiveness, up to 11 years, has been assessed in several studies, and consistently showed a decrease over time [Schmader, 2012b; Morrison, 2015; Tseng, 2016; Baxter, 2017]. While *Zostavax* offers the opportunity for prevention of HZ, its efficacy is not consistent across all age ranges, and effectiveness wanes to non-significant levels 8 to 11 years after vaccination (refer to Section 1.1.2.2 for details). In addition, *Zostavax* is contraindicated in individuals who are immunosuppressed or immunodeficient because it is a live attenuated vaccine.

Prevention of HZ by a non-live vaccine that would offer high and long-term protection that is consistent across all age groups could further help to limit the burden of illness (BoI) caused by HZ and its complications. Therefore, the HZ/su vaccine has been developed to address this significant remaining unmet medical need in the prevention of HZ.

HZ/su, a recombinant subunit vaccine, has been designed to restore VZV immunity in individuals who are at increased risk of developing HZ due to age or immunodeficiency. The age-related decline in VZV-specific cell-mediated immunity (CMI) is correlated to an increase risk of HZ [Cohen, 2013; Weinberg, 2009]. Therefore, VZV-specific CMI is s likely to be a prerequisite to prevention of acquiring HZ. Although the precise mechanism that prevents reactivation of VZV remains unknown, it is plausible that antibodies are also required for the efficient elimination of infected cells, through a

mechanism referred to as to antibody-dependent cell-mediated cytotoxicity [Kamiya, 1982; Tilden, 1986; Arnold, 2017]. In order to prevent re-activation of VZV, an effective vaccine should therefore enhance both the CMI and humoral immune responses in the target population. HZ/su was specifically designed to address these challenges through the unique combination of the VZV surface glycoprotein E antigen (gE) and the Adjuvant System (AS)01_B. gE provides specificity to the immune response against VZV while $AS01_B$ enhances gE-specific immune response, which is pre-existing in VZV-exposed individuals. Additionally, the use of an adjuvant system in combination with the antigen is intended to induce a durable response and long-lasting protection. HZ/su is therefore expected to provide an important benefit to older adults at risk for developing HZ due to their weakened immune systems, regardless of their age.

Finally, as HZ/su is a non-live vaccine, it is not anticipated to be contraindicated in immunocompromised (IC) individuals. A clinical development program evaluating HZ/su in subjects with a variety of immunocompromising conditions is currently ongoing. This program is not complete and is not meant to support the current proposed indication.

Vaccine Design and Composition

HZ/su consists of the recombinant subunit varicella zoster virus (VZV) glycoprotein E (gE) and $AS01_B$.

The gE antigen is produced by recombinant DNA technology in Chinese Hamster Ovarian cells (CHO) and is provided in a lyophilized form in monodose vials (50 µg/dose). VZV gE was selected as the vaccine antigen for HZ/su due to its essential role in VZV replication and cell-to-cell spread [Zerboni, 2014]. Importantly, it is expressed in neural ganglia and skin lesions during viral reactivation and HZ episodes [Cohen, 2013]. gE is also a natural target for the immune system and individuals who have been previously exposed to VZV have a cell-mediated and humoral immunological response to gE [Arvin, 2008].

The $AS01_B$ Adjuvant System is a liposome-based adjuvant containing 50 µg of each of the immuno-enhancers *Quillaja saponaria* Molina, fraction 21 (QS-21) and 3-*O*-desacyl-4'-monophosphoryl lipid A (MPL). $AS01_B$ is provided in a liquid form in separate monodose vials (0.5 ml/dose). The content of the $AS01_B$ vial is used to reconstitute the content of the gE vial prior to intramuscular injection of HZ/su.

The selection of AS01 was based on its ability to induce antigen-specific CMI responses when combined with various antigens. AS01 has been clinically tested in several candidate vaccines and increased CMI has been consistently observed, regardless of the antigen used [Didierlaurent, 2017]. Non-clinical studies conducted in mice confirmed that AS01 was superior at inducing gE-specific CMI as compared to other GSK Adjuvant Systems or to Aluminum salts [Fochesato, 2016].

The mechanism of action of AS01 has been studied in several animal models. It is the specific combination of MPL and QS-21 that induces effective cellular immunity. gE-specific T-cell responses are significantly higher when MPL and QS-21 were combined

in the liposome as compared to liposome with individual components [Dendouga, 2012]. AS01 induces a transient activation of the innate immune system via signalling pathways specific to MPL (toll-like receptor 4, TLR4) and QS-21 (caspase-1) in draining lymph node resident cells, in particular, macrophages [Didierlaurent, 2009; Detienne, 2016]. . This specific combination creates a local environment that favors the activation of antigen-presenting cells that can specifically stimulate antigen-specific T-cells [Didierlaurent, 2014]. Antigen-specific activated T cells in turn can support the differentiation of cognate B cells and consequently increase antigen-specific antibody responses. Use of specific depletion models demonstrated that the transient activation of the innate immune system by AS01, in particular of specific cytokines and antigen presenting cells, is critical to achieve a significant level of CMI and antibody response to gE. The mechanism of action of AS01 is further detailed in Section 2.3.2.

Overview of the Clinical Development Program (CDP)

The studies included in the Biological Licence Application (BLA) submitted to the US Food and Drug Administration (FDA), were designed to support the indication of HZ/su as a prophylactic vaccine for the prevention of HZ in individuals ≥50 YOA. The BLA included data from 19 clinical studies completed at the time of submission. Seventeen of these studies were conducted in individuals ≥50 YOA and included >17,000 subjects who received HZ/su. The other 2 studies (Phase I/II) submitted were conducted in IC populations ≥18 YOA.

In this document, data are presented from: (i) Phase II studies to inform the decisions for the selection of the vaccine formulation and schedule, (ii) 2 pivotal Phase III efficacy and safety studies which form the primary basis of the BLA submission package, and (iii) studies supporting other specific claims in the adult population ≥50 YOA such as co-administration with flu vaccine and schedule flexibility.

Vaccine Formulation and Schedule (Phase II)

Two phase II studies have been conducted in the older adult population for the determination of the antigen dosage, the adjuvant dosage and the number of doses required to ensure both robust CMI and humoral immune responses while maintaining an acceptable safety profile. These studies are briefly described below:

- **ZOSTER-003** evaluated the safety and immunogenicity of three treatment groups that received two doses of vaccine administered two months apart with varying amounts of gE antigen (25 µg, 50 µg, and 100 µg) combined with $AS01_B$, a fourth treatment group receiving a single dose of 100 µg gE combined with $AS01_B$ and a fifth treatment group receiving two doses of 100 µg of gE without adjuvant. The study was conducted in subjects ≥60 YOA.
- **ZOSTER-010** evaluated the safety and immunogenicity of three treatment groups that received two doses of vaccine administered two months apart with varying amounts of adjuvant. 50 µg of the gE antigen was combined with either (i) the full dosage of adjuvant included in HZ/su ($AS01_B$: 50µg MPL, 50µg QS-21), (ii) a half dosage of the adjuvant in HZ/su ($AS01_E$: 25µg MPL, 25 µg QS-21), or (iii) saline.

There was a fourth treatment group receiving only saline. The study was conducted in subjects ≥50 YOA.

In these studies, CMI responses were assessed using an Intracellular Cytokine Staining (ICS) assay, which measured the frequency of gE-specific CD4+ or CD8+ T cells. Humoral immune responses were evaluated through a classical anti-gE Enzyme-Linked Immunosorbent Assay (ELISA). Additional information about the assays used in this and other HZ/su clinical studies are presented in Section 3.3. All the assays used were qualified at the time of study conduct and the validation was subsequently agreed with the Center for Biologics Evaluation and Research (CBER).

Confirmation of the added value of the adjuvant

In **ZOSTER-003**, CMI and humoral immune responses after 2 vaccinations with any dosage of gE adjuvanted with $AS01_B$ were significantly higher than those induced by 2 vaccinations with 100 µg gE/Saline. In terms of CMI responses, the median frequencies of gE-specific CD4[2+] T-cells were similar in all 2-dose gE/$AS01_B$ groups (11.2- to 14.4-fold increase versus pre-vaccination), which were higher compared to the 2-dose 100 µg gE/Saline group (4.2-fold increase). For humoral immune responses, the median anti-gE antibody concentrations were higher in all 2-dose gE/$AS01_B$ groups (29.1- to 41.8-fold increase versus pre-vaccination) compared to the 2-dose 100 µg gE/Saline group (16.1-fold increase). The study therefore confirmed that use of $AS01_B$ led to a statistically significant improvement in the CMI and humoral immunogenicity of gE compared to non-adjuvanted formulations. As anticipated, the inclusion of the adjuvant was associated with an increased frequency in the reporting of local and general solicited symptoms. These were mostly local and self-limiting in duration. There were no safety concerns and all vaccine formulations had an acceptable overall safety profile.

Based on these results and in view of the remaining unmet medical need in the prevention of HZ, it was decided to include the AS01 adjuvant in the formulation for further development in order to obtain optimal efficacy of the vaccine.

Selection of the antigen dose (50 µg gE)

The primary objective of study **ZOSTER-003** was to compare the gE-specific CMI response between different dosages of the gE antigen combined with $AS01_B$, in subjects ≥70 YOA. No significant differences in the CMI responses measured one month after the second dose were observed in subjects ≥70 YOA receiving either 25 µg gE/$AS01_B$, 50 µg gE/$AS01_B$ (HZ/su), or 100 µg gE/$AS01_B$. Similar results were observed in subjects 60-69 YOA. A post hoc sensitivity analyses in which geometric means were adjusted for the CMI pre-vaccination level showed a consistently lower response to 25 µg gE/$AS01_B$ than to 100 µg gE/$AS01_B$ whereas, 50 µg gE/$AS01_B$ (HZ/su) was not inferior to 100 µg gE/$AS01_B$ [Chlibek, 2014]. Hence, 50 µg gE was the lowest dosage of antigen that provided a statistically significantly higher CMI response than the immediately inferior dosage. HZ/su (50 µg gE/$AS01_B$) and the 100 µg gE/$AS01_B$ formulation yielded, a ~30% higher anti-gE antibody concentration than the 25 µg gE/$AS01_B$ formulation, confirming the dosage choice of the 50 µg. There was no apparent relationship between

the dosage of gE and the frequency of solicited AEs. As mentioned above, there were no safety concerns and all vaccine formulations had an acceptable overall safety profile.

The dosage of 50 µg of gE antigen in combination with AS01 (the dose of AS01 was confirmed in a subsequent study) was selected for further development.

Selection of the adjuvant dose ($AS01_B$)

The data from study ZOSTER-010 showed that CMI and humoral immune responses in subjects ≥50 YOA were statistically significantly higher with 50µg gE formulated with $AS01_B$ in comparison to $AS01_E$. The fold increases for the $AS01_B$ formulation over the $AS01_E$ formulations were 1.3- and 1.4-fold for the CMI and humoral immune responses, respectively.

In addition, CMI and humoral immune responses were statistically significantly higher with $AS01_B$ or $AS01_E$ versus no adjuvant. In terms of CMI responses, the median frequencies of gE-specific CD4[2+] T-cells for 50 µg gE/$AS01_B$ (HZ/su) and the 50 µg gE/$AS01_E$ formulation were respectively 5.2- and 4.0-fold higher when compared to 50µg gE/Saline. For humoral immune responses, the median anti-gE antibody concentrations for HZ/su (50 µg gE/$AS01_B$) and the 50 µg gE/$AS01_E$ formulation were respectively 4.7- and 3.4-fold higher when compared to 50 µg gE/Saline. These data confirmed that inclusion of an adjuvant in the HZ candidate vaccine, regardless of the dosage, greatly enhanced the vaccine-induced CMI and humoral immunogenicity.

As expected, a higher rate of solicited symptoms (particularly local solicited symptoms) was observed with the $AS01_B$ adjuvanted vaccine. These were mostly local and self-limiting in duration. There were no safety concerns and all vaccine formulations had an acceptable overall safety profile.

Selection of the two-dose schedule

In **ZOSTER-003**, subjects in all gE/$AS01_B$ 2-dose groups developed significantly higher gE-specific CMI and humoral immune responses than those who received a single dose of 100 µg gE/$AS01_B$. In terms of CMI responses, the median frequencies of gE-specific CD4[2+] T-cells were similar in all 2-dose gE/$AS01_B$ groups (11.2- to 14.4-fold increase versus pre-vaccination), which was higher compared to the 1-dose 100 µg gE/$AS01_B$ group (3.8-fold increase). For humoral immune responses, the median anti-gE antibody concentrations were higher in all 2-dose gE/$AS01_B$ groups (29.1 to 41.8-fold increase versus pre-vaccination) compared to the 1-dose 100 µg gE/$AS01_B$ group (20.3-fold increase). Descriptive data of persistence over 3 years further supports this observation, as the median gE-specific CD4[2+] T-cell frequencies and anti-gE antibody concentrations remained higher in the 2-dose group as compared to the 1-dose group (refer to Section 4.5). These data demonstrate that two doses of HZ/su are required in order to elicit optimal CMI and humoral immune responses in subjects ≥50 YOA.

Conclusion on formulation and schedule

When considering the immunogenicity and safety data from the Phase II studies, in aggregate, the 50 µg gE/$AS01_B$ formulation (HZ/su) in a 2 dose-schedule was selected

for subsequent development. This decision was based on: (i) the demonstration that an adjuvanted subunit approach can induce a high and durable antibody and cellular response against VZV in the target population, (ii) the validation of the antigen (50 µg) and adjuvant ($AS01_B$) dosages and (iii) the observation that HZ/su (50 µg gE/$AS01_B$) formulation had an acceptable safety profile that was comparable to the other adjuvanted formulations tested.

The decision to progress the formulation with the highest dosage of adjuvant was supported by the objective to allow the best probability of success for optimal vaccine efficacy and therefore HZ/su was selected for use in the phase III clinical studies.

Vaccine Efficacy (Phase III)

Efficacy Studies - Design

Two pivotal Phase III efficacy studies, **ZOSTER-006** and **ZOSTER-022**, were conducted in adults ≥50 YOA. Both were randomized, observer-blind, placebo-controlled, multicenter studies to assess the prophylactic efficacy, safety, and immunogenicity of HZ/su when administered according to a 0, 2-month schedule. These studies were conducted concurrently in the same study centers in 18 countries, including the US.

ZOSTER-006 was conducted in subjects ≥50 YOA. Subjects were randomized 1:1 to receive either HZ/su (N=7,698) or saline control (N=7,713). ZOSTER-006 was specifically designed to provide an estimate of VE against HZ in subjects ≥50 YOA (primary objective). Subjects were stratified by age into the 50-59 YOA, 60-69 YOA, 70-79 YOA or ≥80 YOA strata in approximately an 8:5:3:1 ratio to achieve comparable numbers of HZ cases in the 3 main age strata (50-59 YOA, 60-69 YOA, ≥70 YOA). The Final Analysis for VE against HZ was triggered when the pre-specified number of HZ cases needed for analysis had been accumulated, and represents the primary analysis for VE against HZ. The median follow-up period was 3.1 years (range: 0 to 3.7 years) at the time of the Final Analysis. An End of Study (EOS) analysis was performed at the time of the final data lock point of the study and included all cases of HZ and PHN accumulated during the study. The median follow-up period was 4.1 years (range: 0 to 4.5 years) at the EOS analysis.

ZOSTER-022 was conducted in subjects ≥70 YOA. Subjects were randomized 1:1 to receive either HZ/su or saline control (N=6,950 in each group). ZOSTER-022 was specifically designed to provide an estimate of VE against HZ in subjects ≥70 YOA (primary objective). In addition, this study provided substantial additional safety data in subjects ≥70 YOA. The median follow-up period was 3.9 years (range: 0 to 4.5 years) at the time of the ZOSTER-022 analysis (same data lock point as the ZOSTER-006 EOS analysis).

In addition to the individual study endpoints, a series of **pooled analyses** from the 2 studies were also pre-specified, and agreed upon by CBER. These pooled analyses are further referred to as the ZOSTER-006/022 pooled analyses. The pooling of ZOSTER-006 and ZOSTER-022 efficacy data was justified based upon similar study

design between the 2 studies and the random assignment of subjects ≥70 YOA between the studies (i.e., eligible subjects 70-79 YOA and ≥ 80 YOA were randomly assigned to either ZOSTER-006 or ZOSTER-022). The co-primary objectives of the ZOSTER-006/022 pooled analysis were to evaluate the VE against PHN and HZ in subjects ≥70 YOA, across both studies.

The primary cohort for the efficacy analyses was the modified Total Vaccinated Cohort (mTVC). This cohort includes all vaccinated subjects who received two doses of the allocated vaccine in accordance with procedures outlined in the study protocol, and did not develop a case of HZ prior to one month after the second dose. The primary cohort for the safety analyses was the Total Vaccinated Cohort (TVC). This cohort includes all subjects who received at least one dose of HZ/su or saline placebo.

Efficacy Studies – Population

Age is the most common risk factor for developing HZ, this risk further increases with age from 50 YOA onwards. Therefore, the study population included males and females ≥50 YOA in ZOSTER-006 and ≥70 YOA in ZOSTER-022 at the time of the first vaccination. Approximately 20% to 25% of subjects ≥70 YOA in both studies were to be persons ≥80 YOA in order to ensure that this population was adequately represented in the efficacy and safety analyses.

All subjects provided informed consent. Subjects were to be excluded if they had any confirmed or suspected immunosuppressive or immunodeficient conditions or underlying illness that in the opinion of the investigator would be expected to prevent completion of the study (e.g. life-threatening disease likely to limit survival to less than 4 years). Furthermore, subjects had to be without a prior history of HZ or previous vaccination against HZ or varicella.

In the TVC for the ZOSTER-006/022 pooled analysis in subjects ≥50 YOA, similar demographic characteristics were observed in the HZ/su and Placebo groups. The mean age of participants at first vaccination was 68.6 years in both the HZ/su and the Placebo group. There were slightly more female (58.0% and 58.3%) than male (42.0% and 41.7%) participants in the HZ/su and Placebo groups, respectively. In terms of race, the majority of subjects were white (74.3% in the HZ/su group and 74.2% in the Placebo group, respectively), followed by Asian heritage (18.3% in both groups), subjects of other heritage (5.9% and 6.1%, respectively) and subjects of African heritage (1.5% and 1.3%, respectively). In terms of ethnicity, 9.7% and 9.8% of subjects in the HZ/su and Placebo groups, respectively, were of American Hispanic or Latino ethnicity.

In the TVC for North America (US and Canada) in the ZOSTER-006/022 pooled analysis in subjects ≥50 YOA, similar demographic characteristics were observed in the HZ/su and Placebo groups. The mean age of participants at first vaccination was 69.3 years in the HZ/su group and 69.4 years in the Placebo group. There were more female (57.2% and 59.1%) than male (42.8% and 40.9%) participants in both groups. In terms of race, the majority of subjects were white (93.1% in the HZ/su group and 93.0% in the Placebo group, respectively), followed by African heritage (5.8% and 5.2%, respectively), subjects of other heritage (0.5% and 0.9%, respectively) and subjects of Asian heritage

(0.6% and 0.9%, respectively). In terms of ethnicity, 2.8% of subjects in both the HZ/su and Placebo groups were of American Hispanic or Latino ethnicity.

Vaccine Efficacy (ZOSTER-006 and ZOSTER-022)

Studies ZOSTER-006 and ZOSTER-022 included primary objectives for the VE of HZ/su against HZ in adults ≥50 YOA and ≥70 YOA, respectively. The associated statistical success criteria were that the Lower Limit (LL) of the 95% CI for the VE had to be greater than 25% for ZOSTER-006 and greater than 10% for ZOSTER-022. In addition, for the ZOSTER-006/022 pooled analysis there was a co-primary objective for the VE against HZ for those subjects ≥70 YOA. The associated statistical criterion was that the LL of the 95% CI for VE had to be greater than 10%. Prior to evaluation of the primary efficacy hypothesis for the pooled ZOSTER-006/022 dataset, the primary hypothesis for the efficacy of HZ/su against HZ had to be successfully met in ZOSTER-006 for adults ≥50 YOA and in ZOSTER-022 for adults ≥70 YOA, in order to control the Type I error in the statistical analyses.

The VE of HZ/su against PHN in adults ≥70 YOA was also a co-primary objective for the ZOSTER-006/022 pooled analysis. The associated statistical criterion was that the LL of the 95% CI for VE had to be greater than 0. The VE against PHN in ZOSTER-006 for subjects ≥50 YOA and in ZOSTER-022 for subjects ≥70 YOA were secondary objectives in the respective studies.

In the 2 pivotal Phase III efficacy studies, a total of 14,759 and 13,163 subjects from ZOSTER-006 (Final Analysis) and ZOSTER-022, respectively were part of the mTVC and were evaluated in the primary analyses for VE. Of these subjects, 7,344 and 6,541 were in the HZ/su groups of ZOSTER-006 and ZOSTER-022, respectively.

VE against HZ in adults ≥50 YOA

In ZOSTER-006, VE against HZ in subjects ≥50 YOA was 97.2% at the Final Analysis, with 6 confirmed HZ cases in the HZ/su group and 210 in the Placebo group (Table 1). The primary objective of ZOSTER-006 was met (LL of the 95% CI >25%). Similar VE against HZ was observed for all age strata, where the VE estimate was consistently observed to be above 96%. These secondary confirmatory objectives were met (LL of the 95% CI >10%).

Table 1 ZOSTER-006 (Final Analysis): Vaccine efficacy against first or only episode of HZ during the entire study period in adults ≥50 YOA, overall and by age strata (mTVC)

Age strata	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥50 YOA **	**7344**	**6**	**23297.0**	**0.3**	**7415**	**210**	**23170.5**	**9.1**	**97.2**	**93.7**	**99.0**
50-59 YOA *	3492	3	11161.3	0.3	3525	87	11134.7	7.8	96.6	89.6	99.4
60-69 YOA *	2141	2	7007.9	0.3	2166	75	6952.7	10.8	97.4	90.1	99.7
≥70 YOA**	1711	1	5127.9	0.2	1724	48	5083.0	9.0	97.9	87.9	100

N = number of subjects included in each group
n = number of subjects having at least one confirmed HZ episode

Of note, an additional analysis of VE in adults ≥60 YOA (pre-specified in the Statistical Analysis Plan prior to the final analysis) was conducted to evaluate VE in the target population covered by the current ACIP recommendation for HZ vaccination, and the VE was shown to be 97.6% (95% CI: 92.7, 99.6).

VE against HZ in adults ≥70 YOA

Analysis of VE against HZ in subjects ≥70 YOA using pooled ZOSTER-006/022 data was a pre-defined co-primary objective of the pooled analysis and provides the most accurate estimate in this age group. The VE against HZ in subjects ≥70 YOA in the pooled dataset was 91.3%, with 25 confirmed HZ cases in the HZ/su group and 284 in the Placebo group (Table 2). The co-primary objective was met (LL of the 95% CI >10%). Similar VE against HZ was observed for both the 70-79 YOA and ≥80 YOA strata, where the VE estimate was consistently observed to be above 91%.

Table 2 ZOSTER-006/ 022 pooled analysis: Vaccine efficacy against first or only episode of HZ during the entire study period in adults ≥70 YOA, overall and by age strata (mTVC)

Age strata	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥70YOA **	**8250**	**25**	**30725.5**	**0.8**	**8346**	**284**	**30414.7**	**9.3**	**91.3**	**86.8**	**94.5**
70-79YOA *	6468	19	24410.9	0.8	6554	216	24262.8	8.9	91.3	86.0	94.9
≥80YOA *	1782	6	6314.6	1.0	1792	68	6151.9	11.1	91.4	80.2	97.0

N = number of subjects included in each group
n = number of subjects having at least one confirmed HZ episode

In the ZOSTER-022 analysis, the overall VE against HZ in subjects ≥70 YOA was 89.8% (95% CI: 84.2, 93.7) which is consistent with the VE estimate from the ZOSTER-006/022 pooled analysis. The primary objective of ZOSTER-022 was met (LL of the 95% CI >10%).

VE against HZ over time

The large sample size of ZOSTER-006 and ZOSTER-022 as well as the sufficiently long follow-up in these studies allowed for the evaluation of the VE against HZ over successive yearly follow-up periods. This analysis was performed up to 4 years after vaccination (median follow-up was 4.1 years in ZOSTER-006 and 3.9 years in ZOSTER-022). Analysis of VE against HZ over time was performed at the ZOSTER-006 EOS in subjects ≥50 YOA and on the pooled ZOSTER-006/022 data in subjects ≥70 YOA. In both age categories, VE was maintained throughout the period evaluated (i.e., to the 4th year following vaccination). In subjects ≥50YOA, VE against HZ was 98.4% (95% CI: 90.6, 100) during the 1st year and 93.1% (95% CI: 81.2, 98.2) during the 4th year after vaccination. In subjects ≥70 YOA, VE against HZ was 97.6% (95% CI: 90.9, 99.8) during the 1st year and 87.9% (95% CI: 73.3, 95.4) during the 4th year after vaccination.

VE against HZ by region, gender, race and ethnicity

The VE against HZ by region and gender was determined for subjects ≥50 YOA (ZOSTER-006) and ≥70 YOA (ZOSTER-006/022 pooled analysis) and was shown to be consistent with the overall VE against HZ. The VE against HZ by race and ethnicity was determined for subjects ≥70 YOA (ZOSTER-006/022 pooled analysis) and was shown to be consistent with the overall VE against HZ.

Vaccine efficacy against PHN in adults ≥70 YOA

The pooled ZOSTER-006/022 analysis is the primary analysis supporting the overall VE against PHN in adults ≥70 YOA (a pre-defined co-primary objective of the pooled analysis). VE against overall PHN in adults ≥70 YOA was 88.8% (95% CI: 68.7, 97.1), with 4 PHN cases in the HZ/su group and 36 in the Placebo group (Table 3). The co-primary objective of the pooled ZOSTER-006/022 analysis was met (LL of the 95% CI >0%). Furthermore, VE against PHN was 93.0% (95% CI: 72.4, 99.2) in the 70-79 YOA stratum and 71.2% (95% CI: <0, 97.1) in the ≥80 YOA stratum (where the LL of the 95% CI was <0% due to the low number of PHN cases, i.e., 2 PHN cases in the HZ/su group and 7 in the Placebo group).

Results on VE against PHN in subjects ≥70 YOA in the ZOSTER-022 analysis are consistent with the results obtained in the pooled analysis for this endpoint.

Table 3 ZOSTER-006/022 pooled analysis: Vaccine Efficacy against first or only episode of PHN during the entire study period in adults ≥70 YOA, overall and by age strata (mTVC)

Age strata	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥70YOA **	**8250**	**4**	**30760.3**	**0.1**	**8346**	**36**	**30942.0**	**1.2**	**88.8**	**68.7**	**97.1**
70-79YOA *	6468	2	24438.8	0.1	6554	29	24660.4	1.2	93.0	72.4	99.2
≥80YOA *	1782	2	6321.5	0.3	1792	7	6281.6	1.1	71.2	<0	97.1

N = number of subjects included in each group
n = number of subjects having at least one confirmed HZ episode

The vaccine efficacy in further reducing the incidence of PHN in subjects who developed HZ (secondary objective of the pooled analysis) was not statistically significant, due to the low number of HZ breakthrough cases.

Vaccine efficacy against PHN in adults ≥50 YOA

The analysis of overall VE against PHN in subjects ≥50 YOA was a secondary objective of ZOSTER-006 and for the pooled ZOSTER-006/022 analysis. As the results from the pooled analysis are mainly driven by the efficacy in subjects ≥70 YOA, these are not discussed further.

In ZOSTER-006, the overall VE against PHN in adults ≥50 YOA was 100% (95% CI: 77.1, 100) with no PHN cases in the HZ/su group and 18 in the Placebo group. This secondary objective of ZOSTER-006 was met (LL of the 95% CI >0%). Similar overall VE against PHN was demonstrated in the 50-59 and ≥70 YOA strata, however, overall VE against PHN could not be demonstrated in the 60-69 YOA stratum due to the low number of PHN cases reported in the Placebo group.

Conclusions on HZ/su Vaccine Efficacy

The efficacy results of the pivotal ZOSTER-006 and ZOSTER-022 studies support the proposed indication of HZ/su adults ≥50 YOA, as all the pre-specified confirmatory objectives were met. VE against HZ was 97.2% in subjects ≥50 YOA (ZOSTER-006) and 91.3% in subjects ≥70 YOA (ZOSTER-006/022 pooled analysis). VE estimates were observed to be consistent across all age groups studied, including subjects ≥80 YOA, the population at highest risk of developing HZ.

VE against HZ was shown to be maintained throughout the period evaluated (i.e., to the 4th year following vaccination).

Overall VE against PHN in adults ≥70 YOA in the pooled ZOSTER-006/022 analysis was 88.8%. Note that no cases of PHN occurred in subjects 50-69 YOA while 4 cases of PHN occurred in subjects ≥70 YOA in the HZ/su group across both studies. Because of the high VE against HZ, VE against PHN in subjects with confirmed HZ (secondary

objective in the pooled analysis) could not be demonstrated as result of the low number of breakthrough cases observed in these studies.

Immunogenicity (Phase III)

The immunogenicity evaluations of HZ/su were based on the measurement of CMI and humoral immune responses before and after vaccination with HZ/su, defined as main study endpoints as follows:

- the fold increase at one month after the second dose versus baseline
- the vaccine response [a responder being defined as having a response at one month after the second dose that is either at least 2- or 4-fold (for CMI and humoral responses, respectively) above baseline value in subjects who were seropositive at baseline, or at least 2- or 4-fold (for CMI and humoral responses, respectively) above the cut-off value for seropositivity for subjects who were seronegative at baseline].

Evaluation of CMI responses was the primary objective of the Phase I/II HZ/su clinical studies which were pivotal in determining the final vaccine formulation and dosing schedule. The strategy to focus on CMI responses at this stage of the development was because these responses are believed to be essential for protection against the development of HZ.

Once HZ/su was selected based on the optimal CMI and humoral response as well as an acceptable safety profile, HZ/su immunogenicity was evaluated in terms of CMI in a subset of subjects in ZOSTER-006 only, and more broadly in terms of the humoral immune response as measured by the anti-gE ELISA. Anti-gE ELISA is a validated and robust assay suitable for large-scale use that has shown a positive agreement (i.e. concordance) with the CMI ICS assay in terms of vaccine responders, and also good correlation with a VZV neutralisation assay, which indicates that the antibodies induced by HZ/su have the ability to recognize and interfere with the functionality of the native viral gE glycoprotein. The anti-gE ELISA assay was therefore selected as the primary assay for the phase III studies.

Immunogenicity Data from Phase III Studies (ZOSTER-006 and ZOSTER-022)

The immune response to HZ/su has been characterized in a randomly selected subset of subjects enrolled in the ZOSTER-006 and ZOSTER-022 studies.

Humoral immune responses to gE (ZOSTER-006 and ZOSTER-022)

In ZOSTER-006 and ZOSTER-022, anti-gE antibodies were assessed in the humoral immunogenicity subset. In subjects ≥50 YOA in the ZOSTER-006 analysis (N=1,070), geometric mean concentrations (GMCs) were 41.9-fold higher one month after the second dose of HZ/su when compared to pre-vaccination values and a vaccine response rate (VRR) of 98.5% was achieved.

In subjects ≥70 YOA, in the pooled ZOSTER-006/022 analysis (N=742), GMCs were 34.3-fold higher one month after the second dose of HZ/su when compared to pre-vaccination values and a VRR of 96.6% was achieved.

CMI responses to gE (ZOSTER-006)

In ZOSTER-006, gE-specific CMI responses were assessed in the CMI immunogenicity subset. In subjects ≥50 YOA (N=164), median frequencies of gE-specific CD4[2+] T-cells were 24.6-fold higher one month after the second dose of HZ/su when compared to pre-vaccination values.

In subjects ≥70 YOA (N=52), median frequencies of gE-specific CD4[2+] T-cells were 33.2-fold higher one month after the second dose of HZ/su when compared to pre-vaccination values.

Persistence of the HZ/su Immune Response

ZOSTER-024, an extension study of the Phase II study ZOSTER-003, evaluated the long-term follow-up of CMI and humoral immune responses. Descriptive statistics indicated that both CMI and humoral immune responses to gE were highest at one month after the second dose of HZ/su and then declined until they began to plateau approximately 4 years after the first vaccine dose. The gE-specific CMI and humoral immune responses remained, respectively, 3.8-fold and 7.3-fold above the pre-vaccination immune response levels until approximately six years after the first vaccine dose.

Furthermore, modeling of the HZ/su-induced immune response based on the 6-year persistence data of ZOSTER-024 predicts that vaccine-induced immune responses (gE-specific CMI and humoral immune responses) should remain above pre-vaccination levels for at least 10 years in subjects ≥60 YOA at enrolment and after receiving 2 doses of HZ/su in ZOSTER-003.

In ZOSTER-006 and ZOSTER-022, immunogenicity was evaluated up to 36 months after the second dose was administered. At 3 years after the second dose of HZ/su GMCs remained 9.3- and 7.2-fold above the baseline values in subjects ≥50 YOA (ZOSTER-006) and ≥70 YOA (ZOSTER-006/022 pooled analysis), respectively. In ZOSTER-006, at 3 years after the second dose of HZ/su median frequencies of gE-specific CD4[2+] T-cells remained 7.9- and 7.3-fold above the baseline values in subjects ≥50YOA and ≥70 YOA, respectively. These phase III immunogenicity data confirmed the persistence of the CMI and humoral immune responses observed in the follow-up studies of ZOSTER-003.

Other key immunogenicity data

HZ/su can be administered according to a flexible schedule in which the second dose can be given between and 2 and 6 months after the first dose. This has been demonstrated in study ZOSTER-026 where the success criterion for both the vaccine response rate and the anti-gE GMC ratio were met for the group receiving HZ/su according to a 0, 6-month schedule when compared to the group receiving HZ/su according to a 0, 2-month schedule (refer to Section 6.4.1).

HZ/su can be co-administered with quadrivalent seasonal influenza vaccine. This has been demonstrated in study ZOSTER-004 where no clinically relevant interference in the

immune response of either the HZ/su or the quadrivalent seasonal influenza vaccine antigens was observed when the two vaccines were administered concomitantly (refer to Section 6.4.2).

Administration of HZ/su to individuals who have previously experienced an episode of HZ, in study ZOSTER-033, suggested that the vaccine-induced immune response in these subjects was comparable to the vaccine-induced immune response seen in other studies conducted in subjects ≥50 YOA without history of HZ (refer to Section 6.4.3).

Conclusions on HZ/su immunogenicity

In the phase II program, HZ/su was shown to rapidly increase both CMI and humoral immune responses. This was confirmed in the phase III program. In subjects ≥50 YOA where at one month after the second dose the CMI and humoral immune responses were shown to increase by 24.6-fold and 41.9-fold, respectively, in study ZOSTER-006. In subjects ≥70 YOA, CMI responses were shown to increase by 33.2-fold (ZOSTER-006) and humoral immune responses were shown to increase by 34.3-fold (pooled ZOSTER-006/022 analysis) at one month after the second dose.

Available persistence data out to approximately 6 years after the second dose showed that gE-specific CMI and humoral immune responses remained, respectively, 3.8-fold and 7.3-fold above the pre-vaccination levels in subjects who were ≥60 YOA at the time of vaccination.

OVERVIEW OF SAFETY

The potential toxicity of HZ/su or its components (including $AS01_B$ alone) has been assessed extensively in various non-clinical models according to regulatory guidance. No specific concerns were identified in these non-clinical studies that would preclude the use of AS01 in humans [Destexhe, 2013; Giordano, 2017; Segal, 2015; Segal, 2017]. These ese studies showed dose-dependent and transient changes in systemic parameters such as mild local cell infiltration at injection site and transient changes in temperature and C-reactive protein. These findings are all consistent with the mode of action (transient activation of innate immunity) due to the adjuvant effect of AS01. Further investigation in these models revealed that this inflammation is transient (peak at Day 1 and return to baseline by Days 2-3) at the injection site (muscle) and draining lymph node. The local effect of the adjuvant was further supported by the lack of adjuvant effect on antigens administered with AS01 at the same time but at a different site [Didierlaurent, 2014]. In humans, the systemic effect of AS01 was found to be self-limited, with a transient increase (normalizing within 1-2 days) in a few cytokines in the circulation at low levels, suggestive of a spill-over from local activation [Burny, 2017]. Overall, the nature and kinetics of the inflammatory profile of AS01 as described in these non-clinical models are consistent with the reactogenicity profile of HZ/su observed in clinical studies. As for any vaccine containing an adjuvant, a theoretical risk of induction/exacerbation of (pre-existing) inflammatory and/or autoimmune conditions cannot be excluded. Considering this and the transient inflammatory profile of AS01 demonstrated in non-clinical experiments, this risk was carefully evaluated in the clinical vaccine safety assessment.

As such, specific information on Potential Immune-Mediated Diseases (pIMDs) was collected in all HZ/su clinical studies.

Safety data from the Phase III studies ZOSTER-006 and ZOSTER-022

Methodology for safety assessment

In the 17 clinical studies included in the BLA (excluding 2 studies included in the BLA conducted in subjects with IC conditions), >17,000 adults ≥50 YOA received at least one dose of HZ/su. Of these subjects receiving HZ/su, >14,600 were enrolled in the pivotal Phase III efficacy studies ZOSTER-006 and ZOSTER-022. The safety data from these 2 studies were pooled into the 'main safety pooling', as these studies have a similar study design, were conducted concurrently in the same study centers, and contribute to >85% of subjects ≥50 YOA who received HZ/su in the overall safety analysis. Because this pooling includes an adequate control group, a comparative analysis was performed on all safety data of the HZ/su group compared to the Placebo group (saline) in order to assess the relative risk (RR) of reported safety events.

Other studies conducted in subjects ≥50 YOA which had a safety follow-up period of at least 1 year post last vaccination were included in the 'broader safety pooling'. This broader safety pooling analysis was a descriptive analysis of safety data (excluding solicited local and general symptoms) of the HZ/su group only (no Placebo group as comparison). It was designed for the purpose of additional safety signal detection and evaluation of SAEs, fatalities and pIMDs. However, as the safety conclusions on SAEs, fatalities and pIMDs from the broader safety pooling analysis are consistent with those from the main safety pooling analysis, data from the broader safety pooling are not discussed here.

In ZOSTER-006 and ZOSTER-022, solicited local and general symptoms were recorded for 7 days after each vaccination on a 7-day diary card by a subset of subjects, referred to as the 7-day diary card subset (4,884 subjects receiving HZ/su and 4,880 subjects receiving Placebo). The subjects were asked to complete the 7-day diary card daily by indicating if they experienced pre-defined solicited local symptoms (pain, redness and swelling) and general symptoms (fatigue, gastrointestinal symptoms [including nausea, vomiting, diarrhea and/or abdominal pain], headache, myalgia, shivering and fever [defined as temperature ≥37.5°C/99.5°F and preferably measured orally]). All other AEs occurring during the 30-day post-vaccination period were recorded as unsolicited AEs on a 30-day diary card by the 7-day diary card subset of subjects. Subjects who did not belong to the 7-day diary card subset recorded all AEs occurring during the 30-day post-vaccination period as unsolicited AEs using a 30-day diary card (including the symptoms recorded as 'solicited' by the 7-day diary card subset).

In addition, study personnel used scripts during monthly follow-up contacts throughout the study to collect information on events of interest, including serious adverse events (SAEs) up to Month 14, unsolicited AEs with medically attended visits up to Month 8, and SAEs assessed as related to vaccination by the investigator, fatal SAEs, pIMDs, and HZ cases and HZ-related complications during the entire study period (median safety follow-up of 4.4 years). The theoretical risk of induction/exacerbation of (pre-existing)

inflammatory and/or autoimmune conditions associated with the use of vaccines containing adjuvants was carefully evaluated by using a specific methodology for the collection of pIMDs, which included (i) the use of a pre-defined list of disorders that likely represent an autoimmune or immune-mediated inflammatory process of interest, (ii) the use of a customized Medical Dictionary for Regulatory Activities (MedDRA) query for pIMDs to facilitate the identification in databases, and (iii) the use of a disease-specific questionnaire to guide the investigator on relevant information to be collected. The pre-defined list of pIMDs was developed with and validated by an external panel of experts in the field and agreed with major authorities such as FDA, and has been/is updated whenever deemed needed.

Safety results

In the main safety pooling, as was observed in the Phase II studies with HZ/su, higher rates of solicited local and general symptoms were reported after administration of HZ/su than Placebo, regardless of age. Table 4 and Table 5 present the incidence of solicited local and general symptoms, respectively, reported in the HZ/su and Placebo groups for subjects 50-69 YOA and ≥70 YOA in the main safety pooling. Of note, the incidence of solicited local and general symptoms was lower in subjects ≥70 YOA compared to subjects 50-69 YOA. The majority of symptoms seen with HZ/su were mild to moderate in severity and self-limited, with a median duration of at most 3 days. Furthermore, the compliance with the second vaccine dose was very high in both the HZ/su group (95.0%) and the Placebo group (96.0%). In addition, dropout rates due to non-serious and serious AEs were low in both groups (<0.4% during the entire study due to non-serious AEs, and <0.5% up to Month 3 and <4.9% during the entire study period due to SAEs).

Table 4 Main Safety Pooling Analysis: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period in adults 50-69 YOA and ≥70 YOA (Total Vaccinated Cohort with 7-day diary card)

		50-69 YOA				≥70 YOA			
		HZ/su N=2,626		Placebo N=2,617		HZ/su N=2,258		Placebo N=2,263	
Symptom	**Type**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Pain	All	2248	**85.6**	334	**12.8**	1562	**69.2**	199	**8.8**
	Grade 3	225	8.6	13	0.5	90	4.0	4	0.2
Redness (mm)	All	1012	**38.5**	37	**1.4**	851	**37.7**	27	**1.2**
	>100	71	2.7	0	0.0	70	3.1	0	0.0
Swelling (mm)	All	748	**28.5**	23	**0.9**	519	**23.0**	25	**1.1**
	>100	21	0.8	0	0.0	30	1.3	0	0.0

n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum
Grade 3 pain defined as significant pain at rest which prevented normal activities. Grade 3 redness and swelling defined as redness/swelling with a diameter >100 mm

Table 5 Main Safety Pooling Analysis: Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period in adults 50-69 YOA and ≥70 YOA (Total Vaccinated Cohort with 7-day diary card)

		50-69Y				≥70Y			
		HZ/su N=2,624		Placebo N=2,617		HZ/su N=2,252		Placebo N=2,264	
Symptom	**Type**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Fatigue	All	1347	**51.3**	479	**18.3**	825	**36.6**	326	**14.4**
	Grade 3	178	6.8	33	1.3	79	3.5	17	0.8
Gastrointestinal symptoms	All	538	**20.5**	254	**9.7**	304	**13.5**	172	**7.6**
	Grade 3	40	1.5	17	0.6	26	1.2	10	0.4
Headache	All	1185	**45.2**	487	**18.6**	653	**29.0**	268	**11.8**
	Grade 3	128	4.9	24	0.9	34	1.5	10	0.4
Myalgia	All	1390	**53.0**	345	**13.2**	790	**35.1**	225	**9.9**
	Grade 3	186	7.1	23	0.9	62	2.8	10	0.4
Shivering	All	868	**33.1**	171	**6.5**	439	**19.5**	110	**4.9**
	Grade 3	149	5.7	7	0.3	49	2.2	6	0.3
Temperature (°C)	All	679	**25.9**	84	**3.2**	323	**14.3**	61	**2.7**
	>39.0	11	0.4	5	0.2	3	0.1	3	0.1

n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum
Grade 3 general symptom defined as symptom preventing normal activity. Grade 3 fever (measured by oral, axillary or tympanic route) defined as temperature >39.0°C/102.2°F.

In the TVC of the main safety pooling analysis, at least one unsolicited AE occurring within 30 days of vaccination was reported by 7,393 subjects (50.5%) in the HZ/su group (N = 14,645), and by 4,689 subjects (32.0%) in the Placebo group (N = 14,660). The difference in reported rates of unsolicited AEs between the 2 groups is mainly due to the rates of non-serious reactions which occurred in the first 7 days following vaccination, such as injection site reactions and other local and general symptoms that are commonly associated with vaccination. As mentioned before, these symptoms were recorded as unsolicited AEs on the 30-day diary card by subjects in the main safety pooling who were not part of the 7-day diary card subset (HZ/su group: N = 9,761; Placebo group: N = 9,780). As expected, within the 7-day post-vaccination period, the incidence of unsolicited AEs was higher in the HZ/su group (40.0%) compared to the Placebo group (15.2%), while the incidence during the Days 7-29 post-vaccination period was similar for both groups (21.0% and 22.4%, respectively).

An overview of subjects reporting SAEs, fatal SAEs and pIMDs by time period and age stratum in the TVC is presented in Table 6. The incidence of SAEs, SAEs with fatal outcome and pIMDs was similar in the HZ/su and Placebo groups across both age strata and during all follow-up time periods analyzed. The majority of SAEs, including fatal cases, occurred in subjects ≥70 YOA and the majority of fatal SAEs had a time to onset of longer than 1 year post last vaccination. pIMDs were reported at comparable rates regardless of age stratum and approximately half of the pIMDs occurred with time to onset longer than 1 year post last vaccination. Specific SAEs and pIMDs reported were as expected for the target population of adults ≥50 YOA.

Table 6 Main Safety Pooling analysis: Overview of subjects with SAEs, fatal SAEs and pIMDs by time period and by age stratum (TVC)

	50-69 YOA				≥70 YOA			
	Hz/su N=5887		Placebo N=5887		Hz/su N= 8758		Placebo N=8773	
	n	%	n	%	n	%	n	%
SAEs								
≤30 days post-vaccination	81	**1.4**	79	**1.3**	261	**3.0**	248	**2.8**
≤365 days post-vaccination	367	**6.2**	359	**6.1**	1,115	**12.7**	1,166	**13.3**
Entire post-vaccination follow-up period	433	**7.4**	424	**7.2**	1447	**16.5**	1,521	**17.3**
Fatal SAEs								
≤30 days post-vaccination	3	**0.1**	3	**0.1**	14	**0.2**	18	**0.2**
≤365 days post-vaccination	28	**0.5**	27	**0.5**	125	**1.4**	141	**1.6**
Entire post-vaccination follow-up period	95	**1.6**	100	**1.7**	539	**6.2**	580	**6.6**
pIMDs								
≤30 days post-vaccination	13	**0.2**	14	**0.2**	17	**0.2**	16	**0.2**
≤365 days post-vaccination	33	**0.6**	44	**0.7**	57	**0.7**	61	**0.7**
Entire post-vaccination follow-up period	69	**1.2**	84	**1.4**	110	**1.3**	118	**1.3**

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once

In the target population of adults ≥50 YOA, cardiovascular and cerebrovascular diseases are the major causes of morbidity and mortality and, therefore, these events have been considered to be of special interest. A comparative analysis in the main safety pooling showed that none of the selected groups of major cardiac and cerebrovascular events (Standardised MedDRA Queries) were reported significantly more frequently in either the HZ/su or Placebo group (unadjusted p-value <0.05).

An additional analysis performed on subjects vaccinated in ZOSTER-006 and ZOSTER-022 who had a baseline medical history of pIMDs showed no evidence of exacerbation of pre-existing pIMDs or new onset of pIMDs after vaccination. The majority (~98% in both groups) of subjects with at least one pre-existing pIMD did not experience exacerbation of the pre-existing pIMD or a new onset of a different pIMD after vaccination. In addition, 2.8% of subjects with pre-existing pIMDs in both groups had a possible exacerbation/worsening of the pre-existing pIMD, and <2.4% of subjects with pre-existing pIMDs in both groups reported a new onset of a different pIMD during the entire post-vaccination follow-up period.

Following an assessment of risks of inflammation after exposure to HZ/su, a numerical imbalance in the reporting rate of gout (including gouty arthritis) as unsolicited AE was identified for which a biologically plausible relationship with vaccination cannot be excluded at this point. Within the 30-day post-vaccination period, at least one unsolicited AE of gout or gouty arthritis was experienced by 27 subjects (0.2%) in the HZ/su group and 8 subjects (0.1%) in the Placebo group (RR = 3.4, unadjusted p-value <0.01). Most of these events were non-serious and the vast majority of these subjects had either previous episodes of gout reported in the past medical history or concurrent medical conditions that are known risk factors for developing gout and may have contributed to the occurrence of the reported episode. From first vaccination up to 365 days post

vaccination, SAEs associated with gout or gouty arthritis were reported by 5 subjects (<0.05%) and 1 subject (<0.05%), respectively (RR = 5.0, unadjusted p-value = 0.22). All these SAEs revealed alternative explanations for their occurrence. GSK considers the event of gout to be an AE of interest and plans to include it in the active safety surveillance activities of the proposed Pharmacovigilance Plan.

During the entire study period, 9 HZ breakthrough cases in ZOSTER-006 and 23 HZ breakthrough cases in ZOSTER-022 were reported (i.e., confirmed HZ cases that occurred in the HZ/su group). Five of the breakthrough cases in ZOSTER-022 were associated with HZ-related complications, including 4 cases of PHN and one case with an ophthalmic complication (blurred vision). These breakthrough cases did not show any specific common pattern such as clinical presentation or underlying medical conditions.

In addition to the overall analyses, subgroup analyses have been performed in the TVC of the main safety pooling by race, ethnicity and gender, as well as by age for all 3 subgroups. These analyses showed that the reactogenicity and safety profile of HZ/su in these subgroups was comparable with the overall population.

Analyses for North American subjects (US and Canada) in the main safety pooling showed that the reactogenicity and safety profile of HZ/su was comparable with the overall population of subjects in the main safety pooling.

Other safety aspects

Safety data from the following 4 studies which were not included in the main safety pooling and highlight other safety aspects are presented in the briefing document: ZOSTER-026 (other vaccination schedules, Section 7.6.3), ZOSTER-004 (co-administration with FLU-D-QIV, Section 7.6.4), ZOSTER-033 (subjects with previous HZ, Section 7.6.5). and ZOSTER-007 (lot-to-lot consistency, Section 7.6.6). In addition, HZ/su was well tolerated when administered to IC adults ≥18 YOA (subjects with autologous hematopoietic stem cell transplant in ZOSTER-001 and subjects with human immunodeficiency virus [HIV] infection in ZOSTER-015). Of note, 54% of subjects who received at least one dose of HZ/su in these IC studies were ≥50 YOA.

Overall, safety results from all other individual studies in adults ≥50 YOA included in the CDP were consistent with those from the main safety pooling, and revealed no safety concerns.

Conclusions on HZ/su safety

Over 17,000 adults ≥50 YOA received at least one dose of HZ/su during the CDP. In the main safety pooling (ZOSTER-006 and ZOSTER-022) reported rates of solicited symptoms were higher in the HZ/su group than in the Placebo group. This was as expected and consistent with the described mode of action of HZ/su, with the majority of symptoms being mild to moderate in severity and self-limited (median duration of ≤3 days). Compliance for receipt of the second dose was >95% in the HZ/su and Placebo groups. The incidence of unsolicited AEs reported from Day 7 through Day 29 was comparable between the groups. The reporting rates of SAEs, fatalities and pIMDs were similar in the HZ/su and Placebo groups across both age strata and during all follow-up

time periods analyzed, and the specific events reported were as expected for this age group. The overall safety profile of HZ/su has been well-characterized and found to be acceptable; no safety concerns have been identified in the CDP.

Pharmacovigilance Plan

As part of GSK's approach to pharmacovigilance for HZ/su, a Targeted Safety Study (TSS) using an adequate data source is under development and the feasibility is being assessed to evaluate AEs of special interest (e.g., gout). The sample size will be defined by the specific safety endpoints of interest, which will be identified in agreement with regulatory authorities. Potential methodologies for analysis would include observed/expected analysis and assessment of relative and absolute risk (number of excess cases of a given event in the vaccinated population), if a comparator can be identified. In the absence of a comparator, background rates from the literature will be used.

Additional active safety surveillance activities will be conducted to further monitor the safety profile of HZ/su in accordance with the feedback received from FDA. The active surveillance will enable GSK to further enhance the passive surveillance that will continuously be performed for HZ/su, as well for all other licensed vaccines. To this end, GSK is considering using existing demographic, health and vaccination program information and data collection systems in the US, potentially including the Post-licensure Rapid Immunization Safety Monitoring System (PRISM) to monitor AEs after HZ/su vaccination. These AEs will include, but will not be limited to, a pre-defined list of AEs of interest, which will be defined in agreement with regulatory authorities.

The proposed Pharmacovigilance Plan also includes the activities performed for all licensed GSK vaccines, which enable safety signal detection as the post-marketing safety database continues to build. These activities include systematic and regular review of AEs that GSK receives from spontaneous reports, both on an individual and aggregated basis, and from other sources including the medical and scientific literature. Further elements GSK uses to support the planned pharmacovigilance activities include targeted follow-up questionnaires for AEs of interest, which help to improve the quality and consistency of safety data obtained from the reporter, as well as observed/expected analyses using published background rates to enhance signal detection.

Further Clinical Development

GSK is currently conducting a separate CDP in IC populations, including patients with stem cell transplant and renal transplant, and patients with solid malignant tumors and hematologic malignancies. GSK believes HZ/su has the potential to provide significant benefit to these patients. Most of these data were however not available at the time of the BLA submission (October 2016) and are therefore not discussed here. Once all data from this program are available, GSK will discuss the submission of these data with the FDA.

In addition, ongoing studies for the long-term follow-up of efficacy and immunogenicity, the concomitant administration of HZ/su with Tdap or pneumococcal vaccines, the administration of additional doses of HZ/su, as well as the assessment of HZ/su

administered to subjects who previously received *Zostavax,* will be shared with regulatory authorities once available.

Overall Conclusions

HZ/su has been shown to be highly efficacious with VE against HZ of 97.2% in subjects ≥50 YOA (ZOSTER-006) and 91.3% in subjects ≥70 YOA (ZOSTER-006/022 pooled analysis). The VE estimates were observed to be consistent across all age groups studied and efficacy against HZ was maintained to similar levels over the 4 years of the study. HZ/su was also shown to be efficacious in preventing PHN with an overall VE against PHN of 88.8% in subjects ≥70 YOA (ZOSTER-006/022 pooled analysis). In subjects ≥50 YOA (ZOSTER-006) VE against PHN was 100%, with no case of PHN in the HZ/su group and 18 in the Placebo group.

HZ/su is immunogenic and was shown to rapidly increase both CMI and humoral immune responses which persist above baseline levels out to 6 years post vaccination.

The safety profile of HZ/su has been well characterized and demonstrated to be acceptable. More than 17,000 subjects ≥50 YOA have been exposed to HZ/su during the CDP, with >14,600 of these subjects enrolled in ZOSTER-006 and ZOSTER-022. Solicited local and general symptoms reported within 7 days post vaccination were more frequent in the HZ/su group than in the Placebo group. However, the majority of these symptoms were mild to moderate in severity and self-limited, with a median duration of at most 3 days. The incidence of unsolicited AEs reported from Day 7 through Day 29 was comparable between the groups. Overall, the incidence of SAEs, fatalities and pIMDs was similar for the HZ/su and Placebo groups across age strata and during all follow-up time periods analyzed. Based on the review of available safety data, no safety concerns have been identified. GSK considers the event of gout to be an AE of interest and plans to include it in the active safety surveillance activities of the proposed Pharmacovigilance Plan.

In conclusion, the results support the proposed indication: "*Prevention of HZ in adults ≥50 YOA. By preventing HZ, HZ/su reduces the overall incidence of PHN*". HZ/su offers the same level of protection against HZ across all groups ≥50 YOA that is maintained till at least the fourth year after vaccination. Therefore, HZ/su is expected to provide a substantial clinical benefit, and will help to address the remaining medical need in the population at risk of developing HZ. The higher rates of solicited symptoms in HZ/su recipients were expected and consistent with the described mode of action of HZ/su, with the majority of symptoms being mild to moderate in severity and self-limited (median duration of ≤3 days). The benefit-risk profile of HZ/su will continue to be evaluated through a comprehensive Pharmacovigilance Plan to further monitor AEs after HZ/su vaccination. These AEs will include, but will not be limited to, a pre-defined list of AEs of interest that will be agreed with regulatory authorities. The active safety surveillance, including a TSS, will enable GSK to further enhance the passive surveillance that is continuously performed for all licensed vaccines.

Based on all efficacy, immunogenicity and the overall safety data, GSK considers that the benefit-risk profile of HZ/su is favorable for routine vaccination of adults ≥50 YOA to prevent HZ.

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LIST OF ABBREVIATIONS

Ab	Antibody
ACIP	Advisory Committee on Immunization Practices, United States of America
AE	Adverse event
AML	Acute myeloid leukemia
ANCOVA	Analysis of Covariance
anti-gE	Antibody to gE
APC	Antigen-presenting cell
$AS01_B$	Adjuvant System 01 containing 50 µg MPL, 50 µg QS-21 and liposomes
$AS01_E$	Adjuvant System 01 containing 25 µg MPL, 25 µg QS-21 and liposomes
ATP	According-To-Protocol
BLA	Biologics License Application
CBER	Center for Biologics Evaluation and Research, Food and Drug Administration, United States of America
CD4	Cluster of differentiation marker 4, a marker for T-cell stimulated by antigen peptides presented on Major Histocompatibility Complex II
CD40 L	Cluster of differentiation marker 40 ligand
CDP	Clinical Development Program
CHO	Chinese Hamster Ovarian cells
CI	Confidence Interval
CMI	Cell-mediated immunity
dLN	Draining lymph node
DLP	Data lock point
DOPC	Dioleoyl phosphatidylcholine
ELISA	Enzyme-Linked Immunosorbent Assay
EOS	End of Study
EU	European Union
FLU-D-QIV	GSK's seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine
gE	Glycoprotein E
GMC	Geometric Mean Concentration
GMT	Geometric Mean Titer
GSK	GlaxoSmithKline
HI	Hemaglutinin Inhibition
HIV	Human Immunodeficiency Virus
HZ	Herpes Zoster
HZAC	Herpes Zoster Adjudication Committee, also referred to as HZ Ascertainment Committee
HZO	Herpes Zoster Ophthalmicus
HZ/su	The Herpes Zoster subunit candidate vaccine (50 µg gE/$AS01_B$),. Recombinant subunit (su) candidate vaccine for the prevention of HZ consisting of Varicella Zoster Virus (VZV) glycoprotein E (gE: 50 µg) as antigen and an Adjuvant System ($AS01_B$)
IC	Immunocompromised

ICS	Intracellular Cytokine Staining
IDMC	Independent Data Monitoring Committee
IFN-γ	Interferon gamma
IL-2	Interleukin 2
LL	Lower Limit
LPS	Lipopolysaccharide
LTPS	Long-Term Persistence Sub-study (with *Zostavax*)
MedDRA	Medical Dictionary for Regulatory Activities
mIU	milli International Unit
mL	milliliter
MPL	3-*O*-desacyl-4'-monophosporyl Lipid A
mTVC	modified Total Vaccinated Cohort, i.e., cohort used to assess efficacy with subjects excluded who did not receive 2 doses of HZ/su or who developed a confirmed HZ case prior to 1 month after the second dose
µl	Microliter
µg	Microgram
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PHN	Postherpetic neuralgia
PI	Prescribing Information
pIMD	Potential Immune-Mediated Disease
PT	Preferred Term
QS-21	*Quillaja saponaria* Molina fraction 21
RR	Relative Risk
SAE	Serious adverse event
SCR	Seroconversion Rate
SD	Standard Deviation
SOC	System Organ Class
SPR	Seroprotection Rate
SPS	Shingles Prevention Study
su	Subunit
STPS	Short-Term Persistence Sub-study
TNF-α	Tumor Necrosis Factor alpha
TSS	Targeted Safety Study
TVC	Total Vaccinated Cohort
UL	Upper Limit
US	United States
VE	Vaccine Efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee, United States of America
VRR	Vaccine Response Rate
vs.	Versus

VZV	Varicella Zoster Virus
VZV gE	Varicella Zoster Virus surface glycoprotein E antigen
WHO	World Health Organization
YOA	Years Of Age
ZBPI	Zoster Brief Pain Inventory
ZEST	*Zostavax* Efficacy and Safety Trial

TRADEMARKS

The following are mentioned in this document:

- Fluarix is a trademark of the GSK group of companies.
- Zostavax is a trademark of Merck & Co.

In the body of this document, the names of the vaccines/products and/or medications will be written in *italics*.

1. INTRODUCTION

1.1. Key Product Characteristics

Proposed product name: SHINGRIX is the proposed trade name for the candidate Herpes Zoster subunit (HZ/su) vaccine.

Proposed Indication: HZ/su is a non-live, recombinant vaccine indicated for prevention of Herpes Zoster (shingles) in adults aged 50 years and older. By preventing Herpes Zoster, HZ/su reduces the overall incidence of postherpetic neuralgia.

Dosage Forms and Strengths: HZ/su is presented as a suspension for injection which is supplied as a single-dose vial of lyophilized antigen to be reconstituted with the accompanying vial of adjuvant suspension. A single dose after reconstitution is 0.5 mL.

Dose and Schedule: A full vaccination course consists of two doses administered intramuscularly. The second dose can be administered anytime between 2 and 6 months after the first dose.

Composition: After reconstitution, each 0.5 mL dose contains 50 µg of the recombinant Varicella Zoster Virus (VZV) glycoprotein E (gE), 50 µg of 3-O-desacyl-4'-monophosporyl Lipid A (MPL) and 50 µg *Quillaja saponaria* Molina fraction 21 (QS-21), combined in a liposomal formulation (refer to Section 2.2 for more details on composition).

Storage: The antigen and adjuvant vials should be stored refrigerated between 2° and 8°C (36° and 46°F).

1.1.1. Herpes Zoster Disease Burden

1.1.1.1. Natural history of HZ disease

Herpes Zoster (HZ or shingles) is caused by the reactivation of latent VZV. Primary VZV infection results in varicella (chickenpox), after which VZV becomes latent in neurons of the dorsal root and cranial nerve ganglia [Cohen, 2013]. Reactivation of the latent VZV increases with the increase in impaired immunity associated with advancing age and immunocompromising (IC) conditions [Gershon, 2010].

HZ typically presents as an acute, painful, vesicular eruption distributed along a single dermatome that is preceded by prodromal pain in 70% to 80% of the cases, especially in older adults. The prodromal pain typically lasts for 3-4 days but can last up to one week or even longer and results in more than 14% of patients consulting health care professionals [Yawn 2007]. Other symptoms such as fever, malaise and headache may also occur during the prodromal period. Once the typical dermatomal rash appears, acute local neuropathic pain, including paresthesias, dysesthesias, and pruritus occurs in up to 90% of individuals [Dworkin, 2007]. The rash typically heals in 2-4 weeks but may leave scars or pigmentation changes. The median duration of the acute phase pain is 2 weeks

[Scott, 2006] and can be very severe, disabling, and interfere with the patient's daily activities.

1.1.1.2. Epidemiology of HZ

1.1.1.2.1. Incidence of HZ

Most primary VZV infections occur in childhood, leaving adults susceptible to VZV reactivation. Approximately 99% of the United States (US) population ≥40 Years of Age (YOA) has serologic evidence of previous VZV infection [Kilgore, 2003; Lebo, 2015] and is therefore at risk of developing HZ. In Europe, 90% of individuals are seropositive by the time they are 20-29 YOA [Nardone, 2007]. In South America, Australia and some countries in Asia, primary VZV infection may occur later, but by the fourth decade of life, high levels of VZV seropositivity (>90%) are present [Araújo, 2007; Gidding, 2003; Lee, 1998]. This suggests that globally, the vast majority of adults are at risk for developing HZ and its associated complications.

While it is not known what triggers VZV reactivation and the subsequent development of HZ, it is clear that persons with impaired cell-mediated immunity (CMI) due to advanced age, disease or medical interventions are at increased risk for developing HZ [Cohen, 2013]. Although there is study-to-study variation due to differences in methodology, geography appears to have little impact on the incidence of HZ, which is similar across different regions worldwide [Yawn, 2013a]. Incidence rates range from 3 to 5 per 1,000 individuals in various countries, consistently increasing with age [Kawai, 2014]. Approximately 1 out of 3 US adults develops HZ over the course of their lifetime [CDC, 2008] and worldwide, 68% of HZ cases occur in adults ≥50 YOA [Yawn, 2013a]. Around 1 million individuals in the US suffer from HZ each year, with rates observed to be increasing as the overall US population ages.

Several studies have examined trends in the epidemiology of HZ over long periods of time and have found that the incidence of HZ has increased across all age groups regardless of the presence or absence of national varicella vaccination programs, including a >4-fold increase in the US since 1965 [Kawai, 2014]. In a recent retrospective cohort study, the annual increase in incidence of HZ in American adults ≥55 YOA appears to have leveled off since 2006 [Harpaz, 2015]. In the US, the HZ incidence rate in the 50-59 YOA population is 4.6/1,000 person-years [Insinga, 2005], increasing to rates of 11.1 to 45.1/1,000 person-years in adults ≥60 YOA [Oxman, 2005; Hales, 2013; Langan, 2013].

1.1.1.2.2. Recurrence of HZ

The proportion of recurrent HZ ranges from 1.5% to 3% in observational studies that followed patients with HZ up to 2 years [Helgason, 1996; Weitzman, 2013]. A recent t study in immunocompetent patients ≥ 22 YOA with longer follow-up duration estimates higher proportion respectively 3.2%, 4.4%, 5.7% at 4, 6 and 8 years after initial HZ episode [Yawn, 2011]. Another study, conducted in immunocompetent individuals ≥60 YOA, estimates a proportion of HZ recurrence of 0.6% and 1.2% at respectively 4 and 6 years after initial HZ episode [Tseng, 2012]. These data suggest that the short--term risk of HZ recurrence following a recent initial episode is fairly low among

immunocompetent adults [Tseng, 2012], however not nonexistent. Vaccination of these individuals is therefore still fulfilling a medical need, which is also reflected in the 2008 ACIP recommendations for Zoster vaccination: "Zoster vaccine is recommended for all persons aged >60 years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions."

1.1.1.3. Herpes Zoster complications

HZ complications occur in approximately 25% of persons with HZ and become more frequent with age [Yawn, 2007]. The most common HZ complication is postherpetic neuralgia (PHN), which develops in 10% to 30% of patients with HZ, followed by Herpes Zoster Ophthalmicus (HZO), which occurs in 10% to 20% of HZ patients [Johnson, 2014; Kawai, 2014; Yawn, 2013b; Tran, 2016]. These and other less frequent complications of HZ are described in the sections which follow.

1.1.1.3.1. Postherpetic neuralgia

Postherpetic neuralgia (PHN) is a neuropathic pain condition resulting from nerve damage caused by the reactivation of VZV in the dorsal root ganglia. PHN is defined as pain that persists or occurs after the HZ rash and in most studies and publications, PHN is used to describe pain persisting for more than 90 days after rash onset. Patients with PHN report a wide variety of pain characteristics such as intermittent or continuous, deep or superficial, throbbing, stabbing, aching or burning, intense itching, allodynia, or hyperalgesia [Weinberg, 2007].

The incidence and prevalence of PHN varies depending on the case definition used, the study design, and the age distribution of epidemiological study populations [Johnson, 2014; Kawai, 2014; Yawn, 2013a]. Thus the reported risk for developing PHN has varied from 10% to 30% [Kawai, 2014]. In a pooled analysis of prospective cohort studies of HZ patients ≥50 YOA in 7 countries (Canada, Brazil, Mexico, Argentina, Taiwan, South Korea and Thailand), the risk for PHN was found to be 21%, with an increasing proportion with increasing age. In pre-specified age strata, the risk ranged from 14.0% in adults 50-59 YOA, to 21% in those 60-69 YOA, to 30% in those ≥70 YOA. The risk for developing PHN seems to be similar across geographic regions (Asia, North America and Latin America) [Kawai, 2015].

The predictors of PHN include advancing age, IC conditions, severity and duration of HZ rash, and severity of initial HZ pain [Opstelten, 2007; Christo, 2007; Kawai, 2015]. PHN tends to improve over a period of months, and about 70% to 80% of cases resolve within 1 year. In the remaining 20% to 30% of cases, the pain persists for more than 1 year, and PHN may even persist for several years [Christo, 2007].

1.1.1.3.2. Herpes Zoster Ophthalmicus

HZO is defined as HZ within the ophthalmic division of the fifth cranial nerve. HZO is reported in approximately 10% to 20% of HZ cases and can be categorized further as HZO with or without eye involvement [Yawn, 2013b; Tran, 2016]. Common n manifestations of HZO include keratitis which occurs in two-thirds of patients, and may lead to corneal ulceration. Other corneal complications can occur, including

conjunctivitis, retinitis, optic neuritis and glaucoma [Yawn, 2013b]. Chronic HZO may lead to pain, facial scarring and loss of vision [Volpi, 2007].

1.1.1.3.3. Other complications

Other HZ complications include bacterial super-infection of HZ vesicles (reported in approximately 2% of HZ patients), segmental motor nerve damage including nerves of the face, limb weakness, and other neurological complications such as VZV encephalitis, meningitis (reported in 3% to 5% of HZ patients), and disseminated HZ (reported in approximately 1% of HZ patients) [Dworkin, 2007; Harpaz, 2008; Yawn, 2007]. An increased risk of stroke after HZ has also been described, with odds ratios estimated between 1.23 and 1.63 [Kang, 2009; Langan, 2014; Yawn, 2016, Breuer 2014]. A meta-analysis of 6 cohort studies involving 251,076 HZ patients and 8,462 cases of stroke, estimated a pooled relative risk (RR) of 1.36 (95% confidence interval [CI]: 1.10, 1.67) and suggested that HZ patients have a higher risk of stroke within a short term (3 months) [Yang, 2017]. Another recent meta-analysis of 12 studies showed consistent results suggesting that HZ and HZO are significantly associated with cerebrovascular and cardiovascular events [Erskine, 2017].

1.1.1.4. Risk factors for HZ

1.1.1.4.1. Age

The incidence of HZ increases with age due to immunosenescence. The incidence rate of HZ is relatively constant at 2 to 3 cases/1,000 person-years until 40 YOA, and then increases from 50 YOA onwards, rising with progressing age. More than 65% of HZ cases occur in adults ≥50 YOA. The lifetime risk of developing HZ is estimated to be 25 to 30% and is increased to 50% for those >80 YOA [Yawn, 2007; Johnson, 2010].

Both pain- and non-pain related complications of HZ occur in 20% to 40% of cases, and these also increase with age [Yawn, 2013a]. For instance, the risk of PHN is highest in older adults and globally, PHN occurs in approximately 30% of HZ patients ≥70 YOA [Kawai, 2015].

1.1.1.4.2. Immunocompromising conditions

Immunocompromising conditions, particularly those which adversely affect cellular immunity, increase the risk of developing HZ. Immunocompromising conditions that increase the risk of HZ include hematopoietic malignancies, hematopoietic- and chemotherapy-induced immunodeficiency, Human Immunodeficiency Virus (HIV) infection and treatment with immunomodulating medications. HZ in IC populations represents 8% of all HZ cases [Yawn, 2007], nevertheless, IC patients contribute substantially and disproportionately to the public health burden. This is because IC patients are at higher risk for HZ and HZ complications [Chen, 2014a], the HZ rash tends to be more severe and of longer duration, and they are more likely to develop disseminated HZ affecting multiple visceral organs which may lead to a fatal outcome. Furthermore, IC patients are more likely to develop recurrent HZ episodes [Yawn, 2011].

1.1.1.4.3. Other potential risk factors

Other factors that have been identified as potentially impacting the risk of HZ are gender and race. HZ incidence is higher in women than men [Thomas, 2004, Pinchinat, 2013], and subjects from African ancestry and Hispanic ethnicity seem to be less susceptible to HZ than Caucasians [Schmader, 1995; Chaves, 2007].

1.1.2. Overview of Existing Treatments

1.1.2.1. Treatment of HZ and PHN

Treatment of HZ aims to reduce the duration of the disease and avoid or reduce complications. In immunocompetent adults, antiviral therapy has been shown to decrease the duration of HZ rash and associated severity of pain. However, these benefits, which are modest, have only been demonstrated in patients who received antiviral agents within 72 hours after the onset of rash, which limits their effectiveness [Bruxelle, 2012; Whitley, 2010].

A recent Cochrane review considered all randomized controlled trials of antiviral treatment given within 72 hours after the onset of HZ and found evidence that oral acyclovir does not significantly reduce the incidence of PHN [Chen, 2014a]. They found insufficient evidence to determine the effect of other antiviral treatments. Furthermore, 2 randomized trials have shown that the addition of systemic glucocorticoids to antiviral drugs during the acute phase of HZ does not reduce the incidence of PHN [Whitley, 1996; Wood, 1994].

Treatment of PHN is aimed at controlling symptoms [Johnson, 2014]. There is evidence that both tricyclic antidepressants and the anti-epileptic drugs gabapentin and pregabalin may reduce pain but are often associated with significant side effects [Johnson, 2013]. While conflicting evidence exist on the use of opioids [Johnson, 2014], a recent Cochrane review has concluded that there is no convincing and unbiased evidence of a benefit of oxycodone in treating PHN [McNicol, 2013].

1.1.2.2. Prevention of HZ and PHN

As medical therapy can only offer symptomatic relief, prevention of VZV reactivation represents the best strategy to control HZ and the burden of its complications. At the present time, a live attenuated VZV vaccine *Zostavax* is licensed in the US, the European Union (EU), and several other countries. In the US, *Zostavax* is indicated for prevention of HZ in individuals ≥50 YOA and recommended by the Advisory Committee on Immunization Practices (ACIP) for prevention of HZ and its complications among adults 60 YOA and older [Hales, 2014].

The currently-licensed, live attenuated vaccine for the prevention of HZ, *Zostavax*, has a demonstrated vaccine efficacy (VE) against HZ of 69.8% (95% Confidence Interval (CI): 54.1, 80.6) in those 50-59 years of age (YOA), 51% (95% CI: 44, 58) in those ≥60 YOA, 41% (95% CI: 28, 52) in those 70-79 YOA, and 18% (95% CI: <0, 48) in those ≥80 YOA [*Zostavax* Prescribing Information, 2017].

The long-term efficacy of *Zostavax* has been assessed over different time intervals. The Short-Term Persistence Sub-study (STPS) and Long-Term Persistence Sub-study (LTPS) were undertaken to assess the long-term VE in SPS vaccine recipients followed for 5 years and 7 and 11 years post-vaccination, respectively [Schmader, 2012b; Morrison, 2015]. The mean follow-up time in the Zostavax group of the STPS was 1.36 ± 0.29 years, and 0.98 ± 0.30 years in the placebo group, and the mean follow-up in the LTPS was 3.74 ± 0.75 years for both groups. During these intervals, VE against HZ in adults ≥60 YOA decreased from 51.3% (95% CI: 44.2, 57.6) in SPS to 39.6% (95% CI: 18.2, 55.5) in STPS and 21.1% (95% CI: 10.9, 30.4) in the LTPS; VE against PHN decreased from 66.5% (95% CI: 47.5, 79.2) in SPS to 60.1% (95% CI: <0, 86.7) in STPS and 35.4% (95% CI: 8.8, 55.8) in LTPS, respectively. By year 11 post vaccination, VE was non-significant [Morrison, 2015].

A long-term cohort study of the effectiveness of *Zostavax* has been conducted at Kaiser Permanente Southern California. The effectiveness of *Zostavax* decreased from 68.7% (95% CI: 66.3, 70.9) in the 1st year to 4.2% (95% CI: <0, 25.9) in the 8th year [Tseng, 2016] after vaccination of subjects ≥60 YOA. Another long-term cohort study assessed effectiveness against HZ for 8 years after immunization at Kaiser Permanente Northern California. VE was 67.5% (95% CI: 65.4, 69.5) during the first year after vaccination, waned to 47.2% (95% CI: 44.1, 50.1) during the second year after vaccination, and then waned more gradually through year 8 when VE was 31.8% (95% CI: 15.1, 45.2) [Baxter, 2017].

2. PRODUCT DEVELOPMENT RATIONALE

2.1. Medical Need and Scientific Rationale for Development of the HZ/su Vaccine

Approximately 99% of the US population ≥40 YOA has serologic evidence of previous VZV infection [Kilgore, 2003; Lebo, 2015] and is therefore at risk of developing HZ. Approximately 1 out of 3 US adults develops HZ over the course of their lifetime [CDC, 2008]. The lifetime risk of developing HZ is estimated to be 25–30% and is increased to 50% for those >80 YOA [Johnson, 2010]. Management options for HZ are limited in their effectiveness, particularly for the treatment of the acute pain of HZ and the chronic pain of PHN. While the currently licensed vaccine offers the opportunity for prevention of HZ, its efficacy is not consistent across all age ranges [Oxman, 2005], and its effectiveness wanes to non-significant levels 8 to 11 years after vaccination [Schmader, 2012b; Morrison, 2015; Tseng, 2016; Baxter, 2017]. Therefore, prevention of HZ by a vaccine that would offer high and long-term protection that is consistent across all age groups could further help to limit the burden of illness (BoI) caused by HZ and its complications. Therefore, the HZ/su vaccine has been developed to address this significant remaining unmet medical need in the prevention of HZ.

HZ/su, a non-live, recombinant subunit vaccine, is designed to restore VZV immunity to protective levels in individuals who are at increased risk of developing HZ due to age or immunodeficiency. While the level of VZV-specific antibodies remains stable over time the number and the function of memory VZV-specific T-cells decrease with age [Gershon, 1981; Asanuma, 2000; Levin, 2003; Weinberg, 2010]. This age-related decline

ine in VZV-specific CMI has been correlated to an increased risk of HZ [Weinberg, 2009; Arnold, 2016 Arvin, 2005]. Therefore, VZV-specific CMI is likely to be a prerequisite to the prevention of HZ. Although the precise mechanism that prevents reactivation of VZV remains unknown, it is plausible that antibodies are also required for the efficient elimination of infected cells, through a mechanism referred to as antibody (Ab)-dependent cell-mediated cytotoxicity [Arnold, 2016]. In particular, there is *in vitro* evidence that natural killer (NK) cells can kill VZV- infected fibroblasts through the recognition of specific anti-VZV antibodies on infected cells [Kamiya, 1982; Tilden, , 1986]. NK cells can also be activated by VZV-specific CD4+ T-cells via the secretion of IL-2 [Ito, 1986].

In order to prevent re-activation of VZV, an effective vaccine should therefore enhance both the CMI and humoral immune responses in the target population. HZ/su was specifically designed to address these challenges through the unique combination of the varicella zoster virus surface glycoprotein E antigen (VZV gE) and the Adjuvant System (AS), $AS01_B$. gE provides specificity to the immune response against VZV while $AS01_B$ enhances gE-specific immune response, which is pre-existing in VZV-exposed individuals. Additionally, the use of an adjuvant system in combination with the antigen is intended to induce a durable response and long-lasting protection. HZ/su is therefore expected to provide an important benefit to older adults at risk for developing HZ due to their weakened immune systems, regardless of their age

Finally, as HZ/su is a non-live vaccine, it is not anticipated to be contraindicated in immunocompromised (IC) individuals. A clinical development program evaluating HZ/su in subjects with a variety of immunocompromising conditions is currently ongoing. This program is not complete and is not meant to support the current proposed indication.

2.2. Composition of the Vaccine

2.2.1. Product Description

HZ/su is a preservative-free suspension for intramuscular injection. The vaccine is supplied as a single-dose vial of lyophilized antigen to be reconstituted prior to administration with the accompanying single-dose vial of liquid adjuvant suspension. A single dose after reconstitution is 0.5 mL.

The antigen, which is presented in the form of a sterile white powder, is a recombinant truncate of the VZV glycoprotein E, expressed in Chinese Hamster Ovarian (CHO) cells. After purification, the non-infectious gE antigen component is formulated with excipients, filled into vials, and lyophilized under aseptic conditions.

The adjuvant suspension ($AS01_B$ Adjuvant System) is an opalescent, colorless to pale brownish liquid, composed of 3-O-desacyl-4'-monophosporyl Lipid A (MPL) purified from *Salmonella minnesota* and a saponin molecule (QS-21) purified from plant extract *Quillaja saponaria* Molina, combined in a liposomal formulation. The liposomes are composed of dioleoyl phosphatidylcholine (DOPC) and cholesterol in phosphate-buffered

saline solution. After formulation, $AS01_B$ is sterile-filtered before the filling step into vials.

After reconstitution, HZ/su is an opalescent, colorless to pale brownish liquid. Each 0.5-mL dose is formulated to contain the following active ingredients:

- 50 µg of the recombinant VZV gE,
- 50 µg of MPL, and
- 50 µg of QS-21.

Each dose also contains the following excipients:

- 20 mg of sucrose,
- 4.385 mg of sodium chloride,
- 1 mg of DOPC,
- 0.54 mg of potassium dihydrogen phosphate,
- 0.25 mg of cholesterol,
- 0.160 mg of sodium dihydrogen phosphate dihydrate,
- 0.15 mg of disodium phosphate anhydrous,
- 0.116 mg of dipotassium phosphate, and
- 0.08 mg of polysorbate 80.

2.2.2. Manufacturing and Testing

The HZ/su vaccine components (gE antigen and $AS01_B$ Adjuvant System) are manufactured by GlaxoSmithKline (GSK) Biologicals, Belgium. The production methods and facilities meet the Good Manufacturing Practices (cGMP) requirements of the World Health Organization (WHO), the US Food and Drug Administration (FDA) and the EU Committee for Human Medicinal Products (CHMP). All raw materials used in the manufacture of the vaccine comply with the appropriate quality and safety guidelines.

Quality control tests are carried out at various stages of the production process to control the identity, purity, safety and potency of the vaccine components, and are based on all relevant FDA and International Conference on Harmonization (ICH) guidelines, as well as European Pharmacopoeia and WHO monographs.

2.2.3. Storage and Stability

The lyophilized gE antigen and $AS01_B$ Adjuvant System vials are to be stored refrigerated between 2° and 8°C (36° and 46°F) and protected from light. The stability of the lyophilized gE antigen and $AS01_B$ Adjuvant System is currently monitored according to a stability plan as per ICH requirements/guidelines. Available data demonstrate the stability up to 36 months when stored refrigerated.

After reconstitution, the vaccine should be administered promptly. Before administration, the reconstituted vaccine should be kept refrigerated between 2° and 8°C (36° and 46°F), and should be discarded after 6 hours if not used.

The reconstituted vaccine (or its components; i.e. lyophilized antigen or $AS01_B$) must be discarded if the vaccine has been frozen.

2.3. Scientific Rationale for Vaccine Composition

2.3.1. Choice of the gE Antigen

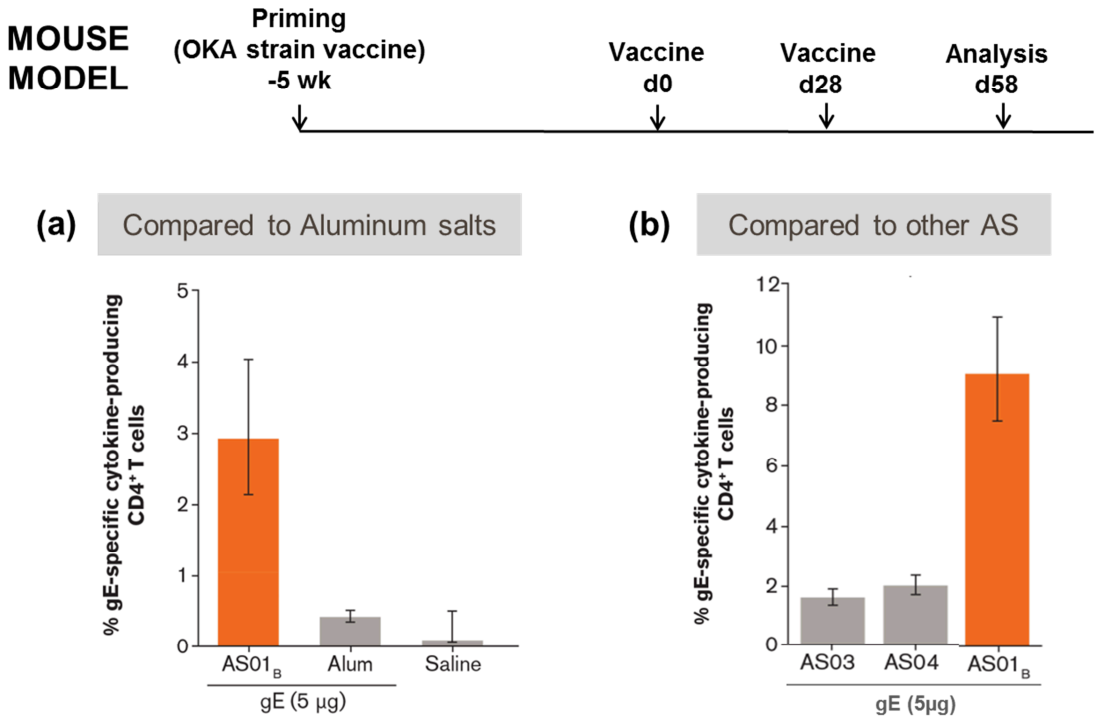
VZV gE was selected as the candidate vaccine antigen for its essential functional role in viral replication and cell-to-cell spread [Zerboni, 2014; Berarducci, 2006; Berarducci, 2009] and because it is a prominent target of the host immune system. In this regard, gE is an abundant VZV glycoprotein expressed on the surface of the virus itself or on virus-infected cells. While gE is not expressed during VZV latency, it is expressed in neural ganglia and skin lesions during viral reactivation and HZ episodes [Lungu, 2006]. gE is also a natural target for the immune system and individuals who have been previously exposed to VZV have detectable gE-specific CMI and Ab levels, making gE a suitable vaccine candidate for the restoration of immunity to VZV [Arvin, 2008; Malavige, 2008; Fowler, 1995].

2.3.2. Rationale for the Selection of AS01 and Summary of Mechanism of Action of AS01

AS01 is part of a family of adjuvants developed by GSK. AS01 was designed more than 20 years ago through a discovery program aimed at combining well-known immunostimulants to be used as adjuvants that improve on aluminum salts, in particular to enhance CMI responses to recombinant antigens, in addition to antibodies [Garçon, 2017]. AS01 has been clinically tested in several candidate vaccines and increased CMI has been consistently observed, regardless of the antigen used. In addition these antigen-AS01 combinations have induced antigen-specific humoral immune responses. These cellular and humoral immune responses are observed regardless of age or specific immune conditions [Didierlaurent, 2017].

The choice of AS01 amongst other Adjuvant Systems was validated in a non-clinical study in mice primed with live-attenuated VZV (OKA strain). The CMI response induced by gE formulated with different Adjuvant Systems, namely AS01 (MPL and QS-21 in liposomes), AS03 (an oil/water emulsion), AS04 (MPL adsorbed on Aluminum salts), or gE adsorbed on Aluminum salts was compared [Dendouga, 2012; Fochesato, 2016]. Four weeks post vaccination, the gE-specific response was measured. gE alone or gE adsorbed on Aluminum salts failed to mount a significant CMI response, hence demonstrating the need for adjuvantation with an alternative Adjuvant System (Figure 1a). When compared to gE/AS03 or gE/AS04, $gE/AS01_B$ induced higher gE-specific CMI response with statistically significant differences noted for all comparisons ($p<0.001$, Figure 1b). AS01 was therefore demonstrated to be the optimal adjuvant to enhance CMI responses to gE. Of note, clinical data comparing AS01 to other Adjuvant Systems when combined with hepatitis B surface (HBs) antigen provided similar conclusions for HBs-specific CMI [Vandepapelière, 2008; Leroux-Roels, 2016].

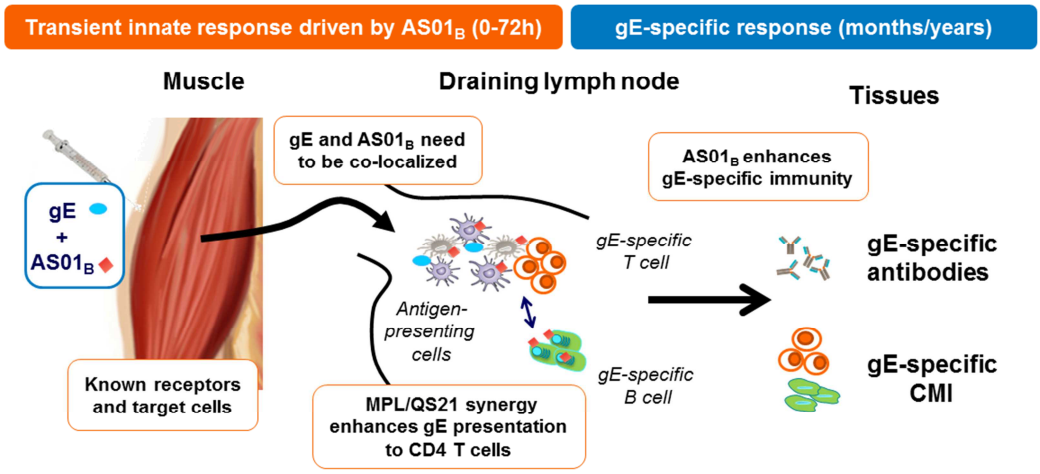
Figure 1 Comparison of gE-specific immune response induced by different adjuvants combined with gE in mice



Spleens were collected from VZV-primed C57Bl/6 female mice, obtained 30 days after the second dose of gE-containing vaccines (with different adjuvants) or saline. MPL and QS-21 were both administered in 5 µg doses. Splenocytes were re-stimulated with a pool of peptides spanning the gE antigen and evaluated using Intracellular Cytokine Staining (ICS). Data are represented as geometric mean responses of gE-specific CD4+ T-cells, expressed as percentages of total frequencies of CD4+ T-cells expressing IFN-γ and/or Interleukin 2 (IL-2), with upper and lower 95% confidence intervals. Figure 1(a): Dendouga, 2012. Figure 1(b): Fochesato, 2016 [https://creativecommons.org/licenses/by/3.0/].

The mechanism of action of AS01 and it components has been studied in different models and recently published [Didierlaurent, 2009; Didierlaurent, 2014; Detienne, 2016, Welsby, 2017; Coccia, 2017; Burny, 2017]. The induction of a durable immune response to vaccine antigens, particularly the T-cell response, requires the stimulation of early inflammatory signals, which efficiently stimulate antigen presentation to cognate T and B lymphocytes [Coffman, 2010; Pulendran, 2006]. In subunit vaccines composed of highly purified recombinant antigens, adjuvants are added to stimulate this early response resulting ultimately in an increased number of activated antigen presenting cells in the lymph node (LN) draining the immunization site. This allows for the efficient stimulation of cognate T cells, which differentiate into long-term immune effectors [Iwasaki, 2010]. In addition, T cells provide help to the differentiation of antigen-specific B cells and contribute to a higher and more sustained antibody response. As described with other adjuvants, we found that AS01 functions following a similar mechanism by inducing a local and transient activation of the innate immune system that is required to promote a long-lasting gE-specific immune response. The key features of AS01 mode of action after intramuscular administration of HZ/su are presented in Figure 2.

Figure 2 Schematic presentation of the mode of action of AS01 after intramuscular administration of HZ/su



Summary of the mode of action of $AS01_B$ in HZ/su [Didierlaurent, 2014; Welsby, 2017; Didierlaurent, 2017; Coccia, 2017].

MPL and QS-21 directly activate innate pathways that are naturally used by the host to recognize pathogens in order to activate the immune system. MPL is recognized by a unique receptor, i.e. Toll-like receptor 4 (TLR4) and can directly stimulate antigen-presenting cells [Didierlaurent, 2009]. MPL is 100 to 1000-fold less potent at inducing cytokines than its parent molecule lipopolysaccharide (LPS), consistent with reduced pyrogenicity to ~0.1% as compared to LPS [Evans, 2003; Coler, 2011]. QS-21 is a water soluble triterpene glycoside recognized by subcapsular macrophages in the lymph node draining the injection site (dLN) where it activates the caspase-1-dependent pathway [Detienne, 2016; Marty-Roix, 2016]. At the cellular level, QS-21 signals through a cholesterol-dependent endocytosis followed by lysosomal destabilization and Syk kinase activation, similar to other adjuvants such as Aluminum salts [Welsby, 2017]. Collectively, the specific recognition of AS01 components by these innate receptors and cells is critical, as depletion of TLR4, caspase-1 or subcapsular macrophages individually have been observed to abrogate the adjuvant effect of AS01 in mouse models.

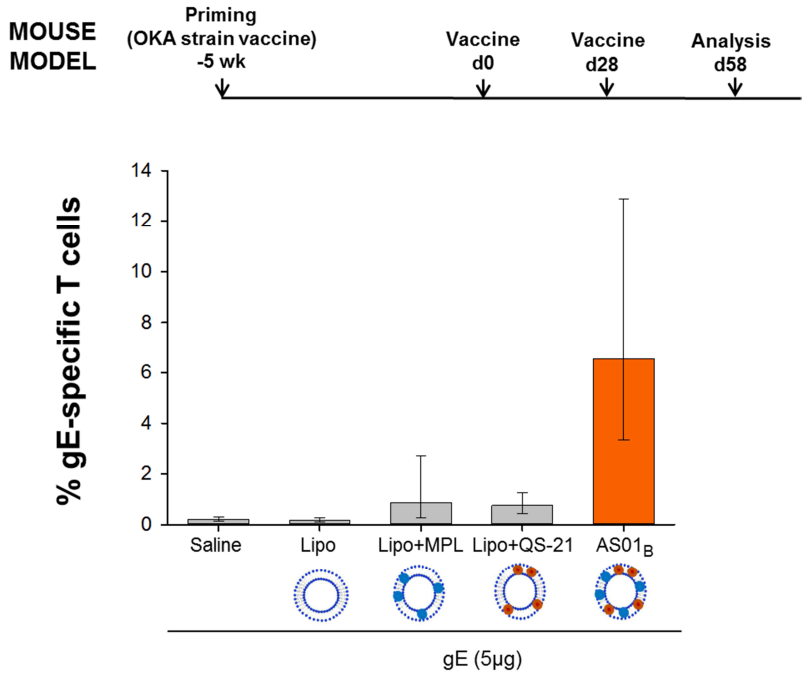
Recognition by specific receptors leads to the activation of the local innate immune system, inducing a transient increase in cytokine production and local innate cell recruitment in the muscle and dLN after rapid drainage of AS01 components. The response is detected as quickly as 3 hours after immunization, peaks on Day 1 or 2 and returns to baseline by Day 7. Cytokine levels were approximately 10-fold lower in the dLNs than in the muscle [Didierlaurent, 2009]. Local inflammatory stimuli increase the frequency of activated antigen-presenting cells (APCs) loaded with gE as well as naïve T and B lymphocytes. This is important as it brings the APC carrying gE and the T and B cells that respond to the APC, together [Didierlaurent, 2009]. gE-specific activated T-cells help the gE-specific B-cells to produce antibodies.

Combining MPL and QS-21 components in AS01 is required to achieve the highest antigen-specific adaptive response against gE (Figure 3) [Dendouga, 2012]. A synergistic effect between MPL and QS-21 is observed for the induction of gE-specific CD4+ T-

cells. Mechanistically, this is explained by an early production of IFN-gamma (IFN-γ) in the dLN that is only observed when MPL and QS-21 are combined [Coccia, 2017]. Blocking early IFN-γ signaling results in a decreased antigen-specific T-cell response, which is associated with a reduced activation of APCs. Overall, the combination of MPL and QS-21 did not lead to a significant increase in inflammation (and in fact resulted in inhibition in some cases) but rather to the emergence of specific pathways that modulated the immune response.

Further investigation described in Coccia *et al* showed important roles for IL-12 and subcapsular macrophage-derived IL-18 in the control of this early IFN signature, a similar pathway used to prevent spreading of lymph-borne bacteria [Kastenmüller, 2012]. Therefore, the unique combination of QS-21 and MPL co-opt a naturally occurring pathway to enhance CMI responses to co-formulated antigens through early IFN-γ production.

Figure 3 MPL and QS-21 are both required to achieve an optimal adjuvant effect



For experimental details, see legend of Figure 1. MPL and QS-21 were both administered in 5 µg doses. Lipo= liposomes. [Dendouga, 2012]

These investigations in pre-clinical models provide explanations for the higher immune response observed with AS01-adjuvanted vaccines as compared to vaccines adjuvanted with other Adjuvant Systems, in particular higher T-cell response [Vandepapelière, 2008; Leroux-Roels, 2016].

3. CLINICAL DEVELOPMENT PROGRAM

The non-clinical data presented above were deemed adequate to support development of the candidate HZ vaccine in humans, as agreed with appropriate regulatory bodies and ethics committees. The Clinical Development Plan was carefully designed and discussed with the FDA and other regulatory authorities throughout the development. Most of the clinical studies were conducted under a US Investigational New Drug application.

3.1. Overview of Studies in the Clinical Development Program

The Biologics License Application (BLA) included data from 19 clinical studies available at the time of submission, in which subjects received HZ/su. Table 1 provides an overview of these 19 studies, including the population in which they were conducted and their main purpose. Of these 19 studies, 17 were conducted in the target population of adults ≥50 YOA and 2 were conducted in IC adults ≥18 YOA.

Data from the following 7 studies are not presented in this briefing document:

- IC studies ZOSTER-001 and ZOSTER-015 as they are not part of the indication currently being sought by this application. A short summary of safety data is provided in Section 7.6.7.
- ZOSTER-023 is a phase I study in adults of Japanese ethnic origin that enrolled a very limited number of subjects with only 6 month safety follow-up post last vaccination and therefore does not contribute significantly to the database.
- ZOSTER-032 as it assessed the use of HZ/su administered subcutaneously and therefore considered not relevant for discussion.
- EXPLO-CRD-004 and its extension studies, ZOSTER-018 and ZOSTER-019, were very early Phase I/II studies for formulation development and vaccination strategy conducted in a limited number of subjects 18-30 YOA and 50-70 YOA.

A more detailed description of the remaining 12 studies included in the BLA and for which data are presented in this briefing document is provided in Appendix Table 1.

Table 1 Overview of studies included in the BLA

Study	Population	Main purpose
ZOSTER-006	≥50 YOA	Pivotal Phase III efficacy and safety study
ZOSTER-022	≥70 YOA	Pivotal Phase III efficacy and safety study
ZOSTER-026	≥50 YOA	0,6 month and 0,12 month vaccination schedules
ZOSTER-007	≥50 YOA	Lot-to-lot consistency
ZOSTER-004	≥50 YOA	Co-administration with seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine
EXPLO-CRD-004 + extension studies ZOSTER-018 and -019	18-30 YOA and 50-70 YOA	Selection of the vaccine formulation and number of doses and immunongenicity persistence
ZOSTER-003 + extension studies ZOSTER-011, -012, -013 and -024	≥60 YOA	Antigen dose-selection study and immunogenicity persistence
ZOSTER-010	≥50 YOA	Adjuvant dose-selection study
ZOSTER-033	≥50 YOA	Immunogenicity and safety in subjects with previous HZ
ZOSTER-023	18-30 YOA and 50-69 YOA	Phase I study for the use of HZ/su in adults of Japanese ethnic origin
ZOSTER-032	≥50 YOA	Subcutaneous administration of HZ/su
ZOSTER-001	≥18 YOA	IC adults with autologous hematopoietic stem cell transplant
ZOSTER-015	≥18 YOA	IC adults with HIV infection

Note: studies indicated in bold text are described in this document

3.2. Inclusion and Exclusion Criteria

The inclusion/exclusion criteria commonly applied across a majority of studies, including the 2 pivotal studies ZOSTER-006 and ZOSTER-022, are listed below.

In order to enter the trials, all subjects had to fulfill the following **inclusion criteria**:

- Subjects whom the investigator believed would comply with the requirements of the protocol (e.g., completion of the diary cards/questionnaires, return for follow-up visits, have regular contact to allow evaluation during the study).
- Written informed consent obtained from the subject.
- A male or female between the ages specified in the protocol at the time of the first vaccination.
- Female subjects of non-childbearing potential could be enrolled in the study.
- Female subjects of childbearing potential may have been enrolled in the study, if the subject had practiced adequate contraception for 30 days prior to vaccination, had a negative pregnancy test on the day of vaccination, and had agreed to continue adequate contraception during the entire treatment period and for 2 months after completion of the vaccination series.

If any of the following **exclusion criteria** applied at the time of study entry, the subject was not to be included in the study:

- Use of any investigational or non-registered product other than the study vaccine(s) within 30 days preceding the first dose of study vaccine, or planned use during the study.

- Concurrently participating in another clinical study, at any time during the study period, in which the subject had been or would have been exposed to an investigational or a non-investigational product.
- Any confirmed or suspected immunosuppressive or immunodeficient condition resulting from disease or immunosuppressive/cytotoxic therapy.
- History of HZ (except ZOSTER-033).
- Previous and/or planned vaccination against varicella or HZ.
- History of allergic disease or reactions likely to be exacerbated by any component of the vaccine.
- Receipt of immunoglobulins and/or any blood products within the 90 days preceding the first dose of study vaccine or planned administration during the study period.
- Administration or planned administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination. However, licensed non-replicating vaccines could be administered up to 8 days prior to each dose and/or at least 14 days after any dose of study vaccine.
- Any other condition that, in the opinion of the investigator, might have interfered with the evaluations required by the study.
- Acute disease and/or fever at the time of enrolment.
- Fever, defined as temperature ≥ 37.5°C (99.5°F) on oral, axillary or tympanic setting, or ≥ 38.0°C (100.4°F) on rectal setting.
- Subjects with a minor illness without fever could be enrolled at the discretion of the investigator.
- Chronic administration (>15 consecutive days) of immunosuppressants or other immune-modifying drugs within 6 months prior to the first vaccination. For corticosteroids, this meant prednisone < 20 mg/day, or equivalent, was allowed. Inhaled and topical steroids were allowed.
- Pregnant or lactating female.
- Female who planned to become pregnant or planned to discontinue contraceptive precautions (if of childbearing potential).
- Significant underlying illness that in the opinion of the investigator would have been expected to prevent completion of the study (specifically for ZOSTER-006 and ZOSTER-022).

3.3. Methods Used to Evaluate Immunogenicity

The immunogenicity evaluations of HZ/su were based on the measurement of CMI (frequencies of gE-specific CD4+Tcells) and humoral immune responses (concentrations of antibodies to gE [anti-gE]) before and after vaccination with HZ/su, in the form of two 2 main study endpoints:

- the fold increase at one month after the second dose versus baseline
- the vaccine response [a responder being defined as having a response at one month after the second dose that is either at least 2- or 4-fold (for CMI and humoral responses, respectively) above baseline value in subjects who were seropositive at baseline, or at least 2- or 4-fold (for CMI and humoral responses, respectively) above the cut-off value for seropositivity for subjects who were seronegative at baseline].

The main assays used in the HZ/su clinical studies to evaluate CMI and humoral immune responses, were the:

gE Intracellular Cytokine Staining (ICS) assay: GSK has developed and validated an ICS assay to measure *in vitro* the frequency of gE-specific CD4+ T-cells in peripheral blood mononuclear cells (PBMCs) isolated from whole blood samples of clinical study participants. The gE ICS assay allows measurement of CMI responses induced by HZ/su by flow cytometry. gE-specific T-cells are defined by detection of at least 2 of the following immune markers: CD40 Ligand (CD40L), Interferon gamma (IFN-γ), Tumor Necrosis Factor alpha (TNF-α), or Interleukin 2 (IL-2) upon stimulation with gE peptides. Frequencies of gE-specific CD4+ T-cells, refered to as "CD4[2+] T-cell" according to the definition above, are expressed as percentages of gE-specific CD4+ T-cells over the total CD4+ T -cells in the PBMC sample.

CMI responses were measured in several clinical studies with HZ/su:

- Phase I/II: CMI responses were evaluated to understand the immunogenicity of the vaccine;
- Phase II: CMI (and humoral) responses were evaluated to establish the optimal vaccine formulation (both antigen and adjuvant doses), and whether 1 or 2 doses would be used;
- Phase III: CMI data were collected in ZOSTER-006, where it was an exploratory objective to confirm the immune response to the vaccine.

Anti-gE Enzyme-Linked Immunosorbent Assay (ELISA): GSK has developed and validated an ELISA to determine the concentration of immunoglobulin G specific to the gE antigen in human serum samples. This assay allows quantitative measurement of the humoral immune response induced by HZ/su. Glycoprotein E is the only VZV-specific antigen in HZ/su. Therefore, assessment of gE-specific immunogenicity is the most appropriate way to confirm immune responses to HZ/su.

The anti-gE ELISA is GSK's core clinical immunological assay for evaluating the humoral immunity induced by HZ/su. In addition to the antibody response, the CMI assay would also be relevant. However, it is a complex assay to implement on large scale, and it requires a substantial blood sampling volume. Therefore, as the objective of the

immune assessment in the phase III program was mainly to monitor that a consistent immune response is generated, the anti-gE ELISA assay was selected. Anti-gE ELISA is a validated and robust assay that has shown a positive agreement (i.e. concordance) with the CMI ICS assay in terms of vaccine responders, and also good correlation with a VZV neutralisation assay, which indicates that the antibodies induced by HZ/su have the ability to recognize and interfere with the functionality of the native viral gE glycoprotein.

Hemagglutinin-inhibition assay

To evaluate the immunogenicity of the seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine used in study ZOSTER-004, Hemagglutinin Inhibition (HI) Ab titers were determined using a GSK validated assay performed as outlined in the method described by the WHO Manual on Animal Influenza Diagnosis and Surveillance, WHO/CDS/CSR/NCS/2002.5, Department of Communicable Disease Surveillance and Response, WHO Global Influenza Programme.

All the assays used were qualified at the time of study conduct and the validation was subsequently agreed with the Center for Biologics Evaluation and Research (CBER).

4. VACCINE FORMULATION AND SCHEDULE (PHASE II)

Two phase II studies, where HZ/su was administered, have been conducted in the older adult population. One of these studies was complemented with extension studies to collect long-term immunogenicity persistence data following administration of HZ/su. These studies determined the antigen dosage, the adjuvant dosage and the number of doses required to ensure both a robust humoral and cellular immune response in vaccine recipients.

4.1. Study Design

4.1.1. ZOSTER-003: Antigen Dosage Selection and Number of Doses

ZOSTER-003 was a phase II, single-blind, randomized, controlled, multi-center vaccination study that evaluated the safety and immune response of HZ/su in older adults aged 60 to 69 YOA and ≥70 YOA. The study compared 3 dosages (25, 50 or 100 μg) of gE with $AS01_B$ adjuvant when administered as 2 doses (at 0, 2 months) compared to 2 doses of 100 μg gE/Saline or a single dose of 100 μg gE/$AS01_B$ to select the optimal antigen dosage and schedule of the candidate HZ vaccine for use in future trials.

A total of 714 subjects were enrolled and randomized in the study, with stratification by age in a 1:4 ratio (60-69 YOA and ≥ 70 YOA). The 5 study groups to which subjects were randomized in a 1:3:3:3:3 ratio were:

- 100 μg gE/Saline, 2 doses (at Month 0 and 2) (N = 54)
- 25 μg gE/$AS01_B$, 2 doses (at Month 0 and 2) (N = 164)
- 50 μg gE/ $AS01_B$ (HZ/su), 2 doses (at Month 0 and 2) (N = 166)

- 100 µg gE/ $AS01_B$, 2 doses (at Month 0 and 2) (N = 165)
- 100 µg gE/ $AS01_B$ (1 dose, Month 0) followed by Placebo (1 dose, Month 2) (N = 165)

Subjects vaccinated in study ZOSTER-003 were offered participation in follow-up studies at Month 12 (ZOSTER-011), Month 24 (ZOSTER-012) and Month 36 (ZOSTER-013) after the first vaccination. Persistence of the CMI and humoral responses were therefore determined for up to 3 years after vaccination for the five study groups. In addition, the HZ/su group was further followed up to Month 72 (ZOSTER-024). Further follow-up is planned for the HZ/su group until 10 years post initial vaccination (ZOSTER-060).

4.1.2. ZOSTER-010: Adjuvant Dosage Selection

ZOSTER-010 was a phase II, observer-blind, randomized, placebo-controlled, adjuvant-dosage selection, multi-center study that evaluated the immunogenicity and safety of 50 µg of the gE antigen combined with either (i) the full dosage of adjuvant included in HZ/su ($AS01_B$: 50µg MPL, 50µg QS-21), (ii) half the dosage of the adjuvant in HZ/su ($AS01_E$: 25µg MPL, 25 µg QS-21), or (iii) saline. There was a fourth treatment group receiving only saline. In all study groups, the vaccine or placebo was administered as 2 doses at 0 and 2 months. The study was conducted in subjects ≥50 YOA.

A total of 410 subjects were enrolled and randomized in the study, with stratification by age with the following ratio: 4:4:3:1 for 50-59 YOA, 60-69 YOA, 70-79 YOA, ≥80 YOA, respectively. The 4 study groups to which subjects were randomized in a 4:4:2:1 ratio were:

- gE/ $AS01_B$= 50 µg gE/ $AS01_B$ (HZ/su), 2 doses (at Month 0 and 2) (N = 150)
- gE/ $AS01_E$ = 50 µg gE/ $AS01_E$, 2 doses (at Month 0 and 2) (N = 149)
- gE/Saline = 50 µg gE/Saline, 2 doses (at Month 0 and 2) (N = 73)
- Saline = Saline, 2 doses (at Month 0 and 2) (N = 38)

4.2. Confirmation of the added value of the adjuvant

In ZOSTER-003, CMI (Figure 4) and humoral (Figure 5) immune responses after 2 vaccinations with any dosage of gE adjuvanted with $AS01_B$ were significantly higher than those induced by 2 vaccinations with 100 µg gE/Saline. This higher response was confirmed to persist for the 3 years all groups were followed up.

Figure 4 **ZOSTER-003 (CMI): Median gE-specific CD4[2+] T-cell frequencies in adults ≥60 YOA up to 36 months post vaccination (ATP cohort for immunogenicity)**

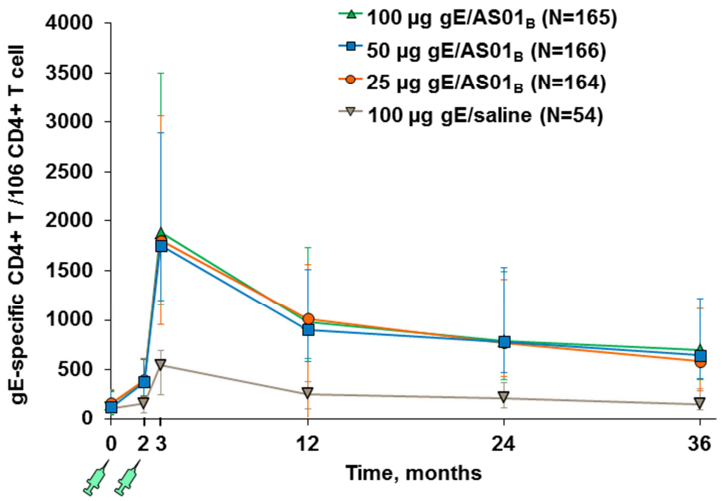
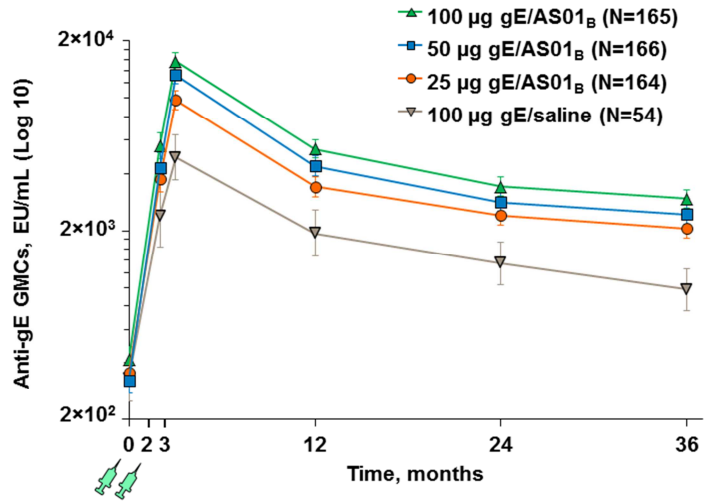


Figure 5 **ZOSTER-003 (Humoral): Geometric mean concentrations of gE-specific antibodies in adults ≥60 YOA up to 36 months post vaccination**



- CMI responses: the median frequencies of gE-specific CD4[2+] T-cells were similar in all 2-dose gE/AS01$_B$ groups (11.2 to 14.4-fold increase versus pre-vaccination), which were higher compared to the 2-doses 100 µg gE/Saline group (4.2-fold increase).
- Humoral immune responses: the median anti-gE antibody concentrations were higher in all 2-dose gE/AS01$_B$ groups (29.1 to 41.8-fold increase versus pre-vaccination) compared to the 2-dose 100 µg gE/Saline group (16.1-fold increase).

The study therefore confirmed that use of $AS01_B$ led to a statistically significant improvement in the CMI and humoral immunogenicity of gE compared to non-adjuvanted formulations.

As anticipated, treatment groups receiving the $AS01_B$ adjuvant had higher rates of solicited symptoms than the group receiving the unadjuvanted vaccine, particularly for local symptoms, which were reported during the 7-day post-vaccination period by 79.9%, 83.1% and 83.0% of subjects receiving 2 doses of 25 µg gE/$AS01_B$, HZ/su and 100 µg gE/$AS01_B$, respectively, and by 31.5% of subjects receiving 2 doses of 100 gE/Saline. These events were predominantly mild to moderate in severity with a maximum median duration of 3 days in the adjuvanted groups. There were no safety concerns and all vaccine formulations had an acceptable overall safety profile.

Based on these results and in view of the remaining unmet medical need in the prevention of herpes zoster, it was decided to include the AS01 adjuvant in the formulation for further development in order to obtain optimal efficacy of the vaccine.

4.3. Selection of the Antigen Dosage (50 µg gE)

The use of 50 µg gE in HZ/su was selected based on the study results of ZOSTER-003.

The primary objective of study ZOSTER-003 was to compare the gE-specific CMI response between the different dosages of the gE antigen combined with $AS01_B$, one month after the second dose in subjects ≥70 YOA. Humoral immune responses were also analysed. Subjects aged 60-69 YOA were also enrolled in this study to evaluate the safety and immunogenicity of the study vaccines in that age group.

When considering the CMI responses at one month after the second dose (Month 3), no significant differences in the CMI responses were observed in subjects ≥70YOA receiving either 25 µg, 50 µg, or 100 µg of gE in combination with $AS01_B$. Similar results were observed in subjects 60-69 YOA. A *post hoc* sensitivity analyses in which geometric means were adjusted for the CMI prevaccination level showed a lower response to 25 µg gE/$AS01_B$ than to 100 µg gE/$AS01_B$ whereas, 50 µg gE/$AS01_B$ was not inferior to 100 µg gE/$AS01_B$ [Chlibek, 2014]. Hence, 50 µg gE was the lowest dosage of antigen that provided a statistically significantly higher CMI response than the immediately inferior dosage (25 µg gE).

Analysis of the antibody response showed that HZ/su (50µg gE/$AS01_B$) and the 100 µg gE/$AS01_B$ formulation yielded a ~30% higher anti-gE Ab concentration than the 25 µg gE/$AS01_B$ formulation, confirming the choice of the 50µg dose.

The dosage of the gE antigen did not significantly impact the rate of at which solicited symptoms were reported. As described in Section 4.2, the inclusion of the adjuvant was associated with an increased frequency in the reporting of local and general symptoms. These were mostly local and self-limiting. No clear relationship was noted between the incidence or severity of overall unsolicited AEs and the dosage of the gE antigen or the presence of $AS01_B$ adjuvant. The incidence of vaccine-related unsolicited AEs appeared to be unrelated of the dosage of gE, whereas they were somewhat more frequent in

groups receiving $AS01_B$ adjuvant. The incidence of serious adverse events (SAEs) was low (<3%) regardless of treatment group and all were considered not related to study vaccine by the investigator. All formulations were shown to have an acceptable overall safety profile.

4.4. Selection of the Adjuvant Dosage ($AS01_B$)

$AS01_B$ was selected based on the study results of ZOSTER-010.

The primary objective of the study was to select the dosage of adjuvant based on the comparison of gE- and VZV-specific CMI and humoral immune responses between 50µg gE/$AS01_B$ and 50µg gE/$AS01_E$ at Month 3 (one month following vaccinations at Months 0 and 2) in subjects ≥50 YOA.

The data showed that CMI (Table 2) and humoral (Table 3) immune responses in subjects ≥50 YOA were significantly higher with gE formulated with $AS01_B$ or $AS01_E$ versus unadjuvanted gE antigen, further confirming that inclusion of an adjuvant in the HZ candidate vaccine, regardless of the dosage, greatly enhanced the vaccine-induced cellular and humoral immunogenicity.

The CMI and humoral responses to gE induced by HZ/su were significantly higher in comparison to those induced by gE/$AS01_E$:

- Two doses of HZ/su induced 30% higher gE-specific CMI than gE/$AS01_E$ at Month 3 (Table 2).
- Two doses of HZ/su elicited higher anti-gE Ab concentrations (40%) than gE/$AS01_E$ at Month 3 (Table 3).

Table 2 ZOSTER-010 (CMI): Fold-increase in geometric mean gE-specific CD4 [2+]T-cell frequencies in subjects ≥50 YOA at one month post last vaccination (Month 3) (ATP cohort for immunogenicity)

Vaccine	Fold increase versus 50 µg gE/$AS01_E$			Fold increase versus 50 µg gE/Saline		
		95% CI			95% CI	
		LL	UL		LL	UL
50 µg gE/$AS01_B$ (HZ/su)	**1.30**	1.07	1.58	5.21	3.89	6.98
50 µg gE/$AS01_E$	-	-	-	4.02	3.00	5.40

Table 3 ZOSTER-010 (Humoral): Fold-increase in geometric mean anti-gE antibody concentrations in subjects ≥50 YOA at one month post last vaccination (Month 3) (ATP cohort for immunogenicity)

Vaccine	Fold increase versus 50 µg gE/AS01$_E$			Fold increase versus 50 µg gE/Saline		
		95% CI			95% CI	
		LL	UL		LL	UL
50 µg gE/AS01$_B$ (HZ/su)	**1.40**	1.17	1.68	4.72	3.81	5.85
50 µg gE/AS01$_E$				3.36	2.72	4.17

As expected, the incidence of any symptoms (solicited or unsolicited) reported during the 7-day post-vaccination period was higher for subjects receiving an adjuvanted vaccine (87.3% and 77.2% of subjects in the HZ/su and gE/AS01$_E$ groups, respectively) compared to subjects receiving gE/Saline or Saline (43.8% and 21.1%, respectively). This increase was most apparent for solicited local symptoms (reported by 84.0%, 71.1%, 23.2% and 7.9% of subjects in the gE/AS01$_B$, gE/AS01$_E$, gE/Saline and Saline groups, respectively), while solicited general symptoms were reported by 63.3%, 55.0%, 32.9% and 18.4% of subjects, respectively. The percentage of subjects who reported unsolicited symptoms during 30 days (Day 0-29) following vaccination was 31%, 25%, 25% and 16% for the gE/AS01$_B$, gE/AS01$_E$, gE/Saline and Saline groups. The corresponding incidences of grade 3 unsolicited symptoms were not different between the groups, and 3.3%, 2.0%, 1.4% and 2.6% respectively. No related SAEs or immune mediated diseases were reported in any of the study groups. All formulations were shown to have an acceptable overall safety profile.

Considering the immunogenicity and safety data generated in the early clinical development program, the HZ/su vaccine formulation (50 µg of gE antigen combined with AS01$_B$ adjuvant) was selected for further clinical development.

4.5. Selection of the Two-dose Schedule

In **ZOSTER-003**, subjects in all gE/AS01$_B$ two-dose groups developed significantly higher gE-specific CMI and humoral immune responses than those who received a single dose of 100 µg gE/AS01$_B$. The CMI (Figure 6) and humoral (Figure 7) immune responses elicited by 2 doses of HZ/su were significantly higher than those of a single dose with a higher amount of antigen. These higher responses were still observed at 3 years post-vaccination. These data demonstrate that 2 doses of HZ/su are required in order to elicit the most optimal and persistent CMI and humoral immune responses in subjects ≥60 YOA.

Figure 6 **ZOSTER-003 (CMI): Median gE-specific CD4[2+] T–cell frequencies in adults ≥60 YOA up to 36 months post vaccination**

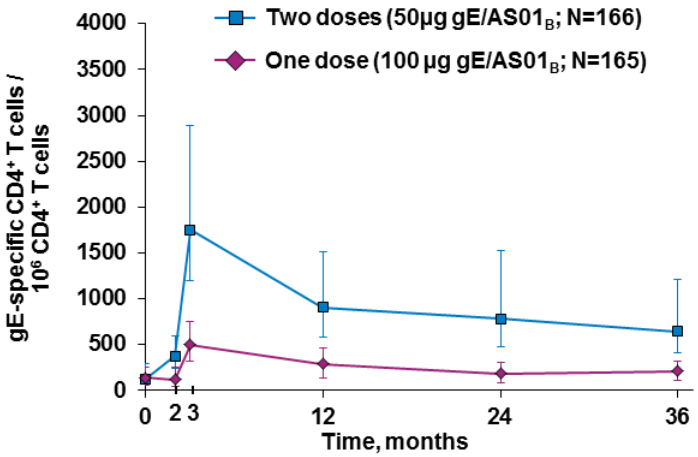
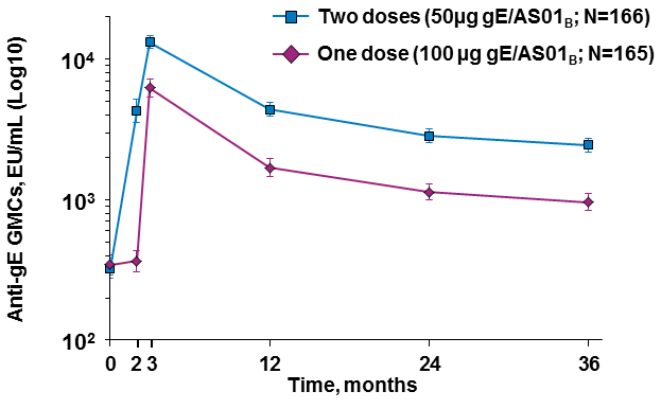


Figure 7 **ZOSTER-003 (Humoral): Geometric mean concentrations of gE-specific antibodies in adults ≥60 YOA up to 36 months post vaccination**



4.6. Conclusion on Formulation and Schedule

When considering the immunogenicity and safety data from the Phase II studies, in aggregate, the 50 µg gE/AS01$_B$ formulation (HZ/su) in a 2 dose-schedule was selected for subsequent development. This decision was based on: (i) the demonstration that an adjuvanted subunit approach can induce a high and durable antibody and cellular response against VZV in the target population, (ii) the validation of the antigen (50 µg) and adjuvant (AS01$_B$) dosages and (iii) the observation that HZ/su (50 µg gE/AS01$_B$) formulation had an acceptable safety profile that was comparable to the other adjuvanted formulations tested.

Given the significant remaining unmet medical need with the current prevention measures, the decision to progress the formulation inducing the highest immune response was based on the higher probability of success for optimal and durable vaccine efficacy in adults ≥50 YOA.

5. VACCINE EFFICACY (PHASE III)

Two pivotal Phase III efficacy studies, ZOSTER-006 and ZOSTER-022, were conducted to evaluate whether HZ/su prevents HZ and PHN in adults ≥50 YOA. Immunogenicity and safety objectives are further discussed in Sections 6 and 7, respectively.

5.1. Key Features of Efficacy Studies

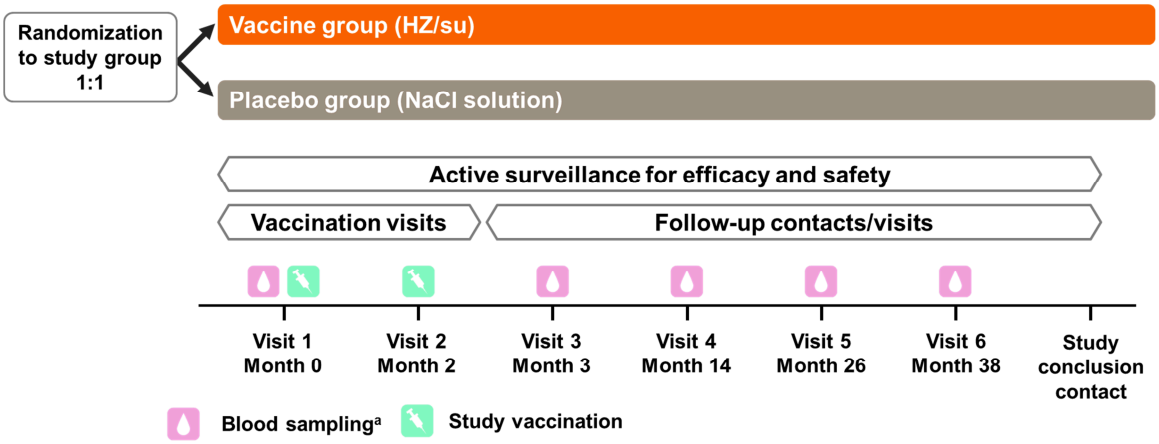
5.1.1. Overview and Discussion of Study Design

The overall study design for ZOSTER-006 and ZOSTER-022 is shown in Figure 8. ZOSTER-006 and ZOSTER-022 were conducted concurrently in all centers of the 18 participating countries. Prior to treatment allocation, subjects 70-79 YOA and ≥80 YOA were randomized to either study ZOSTER-006 or ZOSTER-022. The parallel conduct of the 2 efficacy studies enabled pooling of the study results, which resulted in a larger sample size of adults ≥70 YOA. Importantly, this strategy allowed for the evaluation of key efficacy and safety objectives in the older age strata that are known to be at higher risk for HZ and its associated complications.

ZOSTER-006 was a Phase III, randomized, observer-blind, placebo-controlled, multicenter study conducted in 18 countries including the US, to assess the efficacy, safety, and immunogenicity of HZ/su when administered according to a 0, 2-month schedule in adults ≥50 YOA. The Total Vaccinated Cohort included 15,411 subjects who were randomized 1:1 to receive either the HZ/su or placebo (saline).Subjects Subjects were stratified by age into the 50-59 YOA, 60-69 YOA, 70-79 YOA or ≥80 YOA strata in approximately an 8:5:3:1 ratio, which was estimated to achieve comparable numbers of HZ cases in the 3 main age strata (50-59 YOA, 60-69 YOA, ≥70 YOA). ZOSTER-006 was designed to provide an estimate of VE against HZ in the ≥50 YOA study population (primary objective). The evaluations of VE against HZ in the 3 age strata and VE against overall PHN in subjects ≥50 YOA and by age strata, were secondary study objectives. The Final Analysis for VE against HZ was triggered when the pre-specified number of HZ cases had been accumulated, and represents the primary analysis for VE against HZ. The median follow-up period in the modified Total Vaccinated Cohort (mTVC) was 3.1 years (range: 0 to 3.7 years) at the time of the Final Analysis (i.e., the analysis triggered by achieving the pre-specified number of HZ cases). As foreseen in the protocol, subjects continued to be followed up in the ZOSTER-006 study beyond the DLP for the Final Analysis, in order to further accumulate cases of HZ and PHN for the pooled analyses over both studies as well as for longer safety follow-up. An End of Study (EOS) analysis was performed at the time of the final data lock point of the study and included all cases of HZ and PHN accumulated during the study. The median follow-up period was 4.1 years (range: 0 to 4.5 years) at the EOS analysis.

ZOSTER-022 was a Phase III, randomized, observer-blind, placebo-controlled, multi-center study conducted in 18 countries including the US to assess the efficacy, safety, and immunogenicity of HZ/su when administered according to a 0, 2 -Month schedule in adults ≥70 YOA. The Total Vaccinated Cohort included 13,900 subjects who were randomized 1:1 to HZ/su or placebo (saline).Subjects were stratified by age: 70-79 YOA and ≥80 YOA and were enrolled in approximately a 3:1 ratio (the same age-stratification ratio as was used for these age strata in ZOSTER-006). The 70-79 YOA and ≥80 YOA strata were combined for the primary ≥70 YOA overall analyses and pooled with ZOSTER-006 data for the pooled analysis.

Figure 8 ZOSTER-006 and ZOSTER-022 study designs



Note: In case of suspected HZ, the subject had additional visit(s).
[a]A subset of subjects in ZOSTER-006 were assessed for CMI and humoral immune responses, and in ZOSTER-022 for humoral immune responses only.

5.1.2. Key Study Objectives

The primary objective of ZOSTER-006 and ZOSTER-022 was to evaluate VE in the prevention of HZ compared to placebo in adults ≥50 YOA and ≥70 YOA, respectively, as measured by the reduction in HZ risk.

The co-primary objectives of the ZOSTER-006/022 pooled analysis were to evaluate VE in the prevention of overall PHN and to consolidate the VE estimation in the prevention of HZ compared to placebo in subjects ≥70 YOA across both studies.

Secondary objectives were specified in the ZOSTER-006 and ZOSTER-022 protocols and further clarified in the respective Statistical Analysis Plans (SAPs).

Secondary objectives related to efficacy evaluated in ZOSTER-006 and in ZOSTER-022 were: (i) to evaluate VE in the prevention of HZ by age strata (ZOSTER-006 only); (ii) to evaluate VE in the prevention of overall PHN; (iii) to evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period in subjects with confirmed HZ; (iv) to evaluate VE in the reduction of HZ-related mortality

and hospitalizations in subjects with confirmed HZ; (v) to evaluate VE in the reduction in incidence of HZ-associated complications in subjects with confirmed HZ; and (vi) to evaluate VE in the reduction in use of pain medications in subjects with confirmed HZ.

Secondary objectives related to efficacy evaluated in the pooled analysis of ZOSTER-006 and ZOSTER-022 were: (i) to evaluate VE in the prevention of overall PHN in subjects ≥50 YOA; (ii) to evaluate VE in the prevention of PHN in subjects ≥50 YOA with confirmed HZ; and (iii) to evaluate VE in reducing the total duration of severe 'worst' HZ-associated pain over the entire pain reporting period in subjects ≥70 YOA, with confirmed HZ.

5.1.3. Analysis Plan

The pooled efficacy analyses from the 2 studies were pre-specified in the study protocol of ZOSTER-022. However, the individual primary efficacy hypotheses against HZ in ZOSTER-006 and in ZOSTER-022 had to be successfully met per-protocol before advancing with the ZOSTER-006/022 pooled analysis.

Pooling of ZOSTER-006 and ZOSTER-022 efficacy data was justified based on their similar study design, including: (i) the age stratification of 3:1 between subjects 70-79 YOA and those ≥80 YOA, (ii) the studies were conducted concurrently in the same study centers in 18 countries, and (iii) prior to treatment allocation, subjects 70-79 YOA and ≥80 YOA were randomized to either study ZOSTER-006 or ZOSTER-022. Note that the co-primary objectives of the pooled analysis were only to be tested provided that VE against HZ was demonstrated in each study and no adjustment of significance level was to be made.

Study end, for both studies, was to be triggered as soon as a pre-specified number of confirmed HZ and PHN cases determined to be sufficient to demonstrate the efficacy hypothesis had been collected. It was initially planned that the statistical analyses from both studies would be triggered at approximately the same time. However, as the HZ cases accrued over time, it became clear that ZOSTER-006 would reach the conditions for triggering final analysis of the HZ primary endpoint more than one year prior to those conditions being reached for ZOSTER-022. As a consequence of this observation the analyses of the 2 studies were dissociated. Both ZOSTER-006 and ZOSTER-022 protocols were amended to outline a 2-step approach for the efficacy analysis. The first step was to perform on ZOSTER-006 the analysis to confirm VE against HZ in subjects ≥50YOA (primary objective), once the required number of HZ cases had been captured. This first analysis is referred to as the 'Final Analysis' for ZOSTER-006. At that moment, most results of secondary and exploratory objectives that would not lead to unblinding of the clinical team were also provided. The second step was to perform all remaining analyses of ZOSTER-006, as well as of the ZOSTER-022 and pooled analysis over both studies. This second analysis is referred to as the EOS analysis for ZOSTER-006.

In accordance with the amended criteria, the Final Analysis of ZOSTER-006 to determine the VE against HZ in subjects ≥50 YOA was performed in December 2014. This analysis was performed by external statisticians in order to maintain the study

blinding at the individual subject level for GSK staff involved in the HZ/suproject. A Firewall team was established to ensure study blind was maintained from the Final Analysis database freeze until the EOS database freeze.

5.1.4. Independent Data Monitoring Committee

ZOSTER-006 and ZOSTER-022 were monitored by an Independent Data Monitoring Committee (IDMC) that oversaw the ethical, efficacy and safety aspects of the studies and made recommendations to GSK concerning the continuation, modification, or termination of the studies.

5.1.5. Methods Used to Evaluate Efficacy: Case Definitions

A suspected case of HZ was defined as a new-onset unilateral rash accompanied by pain (broadly defined to include allodynia, pruritus or other sensations) and no alternative diagnosis. Suspected cases were reviewed by a medical professional at the study center and described in specific screens in the case report form. Rashes suspected to be HZ by study staff were photographed, and 3 swabs were taken from the HZ lesions for Polymerase Chain Reaction (PCR) analysis for VZV and β-actin. The β-actin PCR results were used to verify whether a lesion sample was adequate in terms of DNA sampling. All case notes and photographs were reviewed by the Herpes Zoster Ascertainment/Adjudication Committee (HZAC) who were not aware of the PCR result for the suspected cases of HZ.

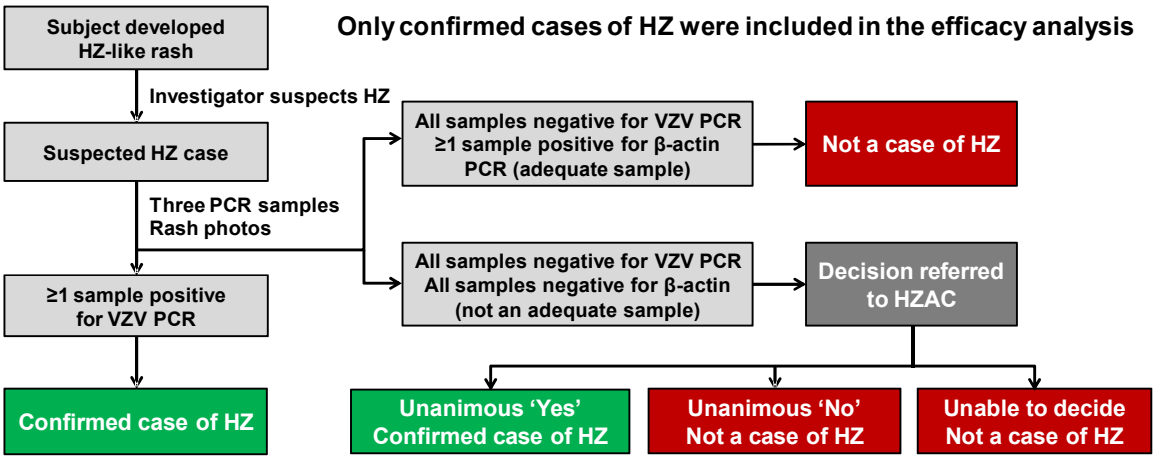
The two PCR assays are GSK validated assays. Briefly, nucleic acids were first extracted from each collected rash swab and then tested with VZV PCR targeting the *orf62* gene. In case of a VZV-negative result after PCR at the subject level, a β-actin PCR was performed on the subject's samples to confirm the validity of the sampling procedure.

Therefore, a suspected case of HZ could be confirmed in 2 ways:

- By PCR on collected rash lesion samples. This was the primary manner in which cases were confirmed as "HZ" or "not HZ".
- By the HZAC who were appointed to classify all referred suspected HZ cases as either "HZ", "not HZ" or "not able to decide." Of note, the classification by HZAC served as the final case definition only when the case could not be confirmed or excluded by PCR. HZAC members were blinded to treatment assignments as well as to PCR results. All decisions of whether a case represented a true HZ diagnosis had to be unanimous by the 5 experts appointed to the HZAC.

The decision tree for classifying a suspected case of HZ is presented in Figure 9.

Figure 9 Flow diagram for HZ case definition



Note: For suspected HZ cases, clinical descriptions by the investigator and photographs were to be captured. This information was used by the HZAC for their assessment of the suspected cases, HZAC did not have access to the PCR results.

The HZ onset date was defined as the earlier of the following 2 events: 1) the HZ rash start date; or 2) the date on which pain at the site of a subsequent HZ rash was first noted. The end date of an HZ episode was defined as the first date at which a subject had no rash (papules, vesicles, ulcers or crusts) present.

A ZBPI questionnaire was used to quantify HZ pain and discomfort and measure selected Activities of Daily Living (ADL) and health in subjects presenting with HZ. The ZBPI was adapted from the Brief Pain Inventory to make it a HZ-specific measure of pain severity that captures pain and discomfort (including allodynia and pruritus) caused by HZ [Coplan, 2004].

Information on HZ-associated pain was derived from the ZBPI question: "Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours" (item 3), which was referred to as "worst pain" in the protocol.PHN was defined by the presence of HZ-associated severe 'worst' pain persisting or appearing more than 90 days after onset of the HZ rash. Severe 'worst' pain was defined as HZ-associated pain rated as 3 or greater on the "worst pain" Zoster Brief Pain Inventory (ZBPI) question. The ZBPI is a validated instrument to assess HZ-associated pain on a 10-point Likert scale, which persists or occurs more than 90 days after the onset of HZ rash [Coplan, 2004; Oxman, 2005]. This case definition was used in the clinical efficacy studies conducted by both Merck and GSK. In each case of suspected HZ, subjects were asked to complete the ZBPI questionnaire daily from the onset of HZ up to 28 days after the onset, and then weekly until HZ-associated pain ceased (defined as a 28-day [or 4-week] pain free period), until at least Day 90 after the onset of symptoms, or until the cut-off date for the EOS analysis in ZOSTER-006 or ZOSTER-022 (whichever came first).

5.1.6. Statistical Methods

5.1.6.1. Data sets analyzed and cohort definitions

The Total Vaccinated Cohort (TVC) included all vaccinated subjects who received at least one dose of HZ/su or Placebo. The TVC for analysis of efficacy included vaccinated subjects for whom data related to efficacy endpoints were available. The primary analysis of efficacy was based on the mTVC for efficacy. The mTVC was defined as all vaccinated subjects who received 2 doses of the allocated vaccine in accordance with procedures outlined in the study protocol, and did not develop a case of HZ prior to one month after the second dose. The mTVC was selected for the primary analysis of efficacy as GSK wanted to assess the VE after subjects had completed the schedule of 2 doses of HZ/su. Subjects who developed a confirmed case of HZ prior to one month after the 2nd dose were also excluded from the analysis in order to give subjects sufficient time to develop a potentially protective immune response following vaccination. The same approach was followed in the vaccine efficacy studies with *Zostavax* [Oxman, 2005; Schmader, 2012a]. An analysis on the TVC for efficacy was planned for sensitivity analyses according to ICH recommendation. The TVC analysis started to count HZ cases from the first vaccination onwards.

5.1.6.2. Analysis of efficacy

The HZ incidence rate was determined with reference to the first confirmed HZ case observed in the subject. The HZ-free period for a subject was calculated from either first vaccination (for TVC) or from one month after dose 2 (for mTVC) to HZ onset date.

The number of person-years at risk over an interval of time was defined as the sum of the confirmed HZ-free periods over all subjects at risk during that interval, either up to the cut-off date for the analysis, the censoring date, or the occurrence of the first HZ case for a subject.

The relative risk (RR) was defined as the ratio of the incidence rates of the HZ/su group over the Placebo group. VE is defined as 1 minus the RR (1 – RR).

Primary inferential analysis for reduction in HZ risk

Because of the large sample size required for the analysis of VE against HZ and PHN, the number of cases in the HZ/su and Placebo groups was approximated by independent Poisson distributions. The primary analysis method of the VE considered the exact inference on the RR stratified for age and regions conditionally to the total number of HZ cases observed and time at risk. RRs were calculated overall and by age strata and region.

In ZOSTER-006, the primary objective regarding HZ VE in subjects ≥50 YOA was demonstrated if the lower limit (LL) of the 95% confidence interval (CI) of VE against HZ was above 25%. The confirmatory primary objective in ZOSTER-006 was assessed at the Final Analysis. Therefore, its re-evaluation at the EOS analysis was only descriptive. Note that ZOSTER-006 was initially not powered to demonstrate statistical significant VE against HZ in subjects ≥70 YOA, since that objective was not within the scope of the study and was deferred to the analysis of ZOSTER-022 and pooled Zoster-

006 and -022 data. In ZOSTER-022, overall HZ VE was demonstrated in subjects ≥70 YOA (primary objective) if the LL of the 95% CI was >10%.

Sensitivity analyses were done by gender, by region and by time after vaccination to assess consistency. The sensitivity analysis of the VE by region was performed to confirm the consistency of the VE across regions. The regions evaluated were Europe, Latin America, North America (US and Canada) and Australia/Asia (defined here as including Australia, Japan, Korea, Taiwan, and Hong Kong). The sensitivity analysis of the overall VE after each multiple of 12-month intervals following last vaccination was performed to assess consistency of VE over time.

Primary inferential analysis for reduction in PHN risk

The overall reduction in PHN risk was evaluated in a similar manner to the risk reduction analysis for HZ risk using the exact inference on the RR stratified for age strata and regions, conditional to the total number of PHN cases observed and the time at risk. Similarly to the HZ VE analysis, a Poisson distribution for the number of PHN cases in the HZ/su and Placebo groups was assumed.

The primary objectives of ZOSTER-006 and ZOSTER-022 (VE against HZ) had to be demonstrated before initiating the analysis of the co-primary objective of the ZOSTER-006/022 pooled data of VE against PHN. A gatekeeping strategy was implemented to show the hypotheses testing scheme that kept the overall type I error (2-sided) controlled at 5% [Dmitrienko, 2007]. Each evaluation in the ZOSTER-006/022 pooled analysis was either preceded by an evaluation in ZOSTER-006, ZOSTER-022, or both; or was only performed on the pooled database during the ZOSTER-006/022 pooled analysis. The ZOSTER-006/022 pooled analysis provided the highest power to generate statistically significant results, and was powered to demonstrate statistically significant PHN VE in subjects ≥70 YOA (primary objective). VE against PHN was demonstrated if the LL of the 95% CI was above 0%. In addition, VE against PHN in subjects ≥50 YOA with confirmed HZ was performed on the ZOSTER-006/ZOSTER-022 pooled data as a secondary objective.

5.2. Efficacy Results

5.2.1. Subject Disposition and Demographic Profile of the Pooled ZOSTER-006 and ZOSTER-022 Study Populations (≥50 YOA)

Across the 2 pivotal Phase III efficacy studies, a total of 14,645 subjects received HZ/su and 14,660 subjects received Placebo. In the ZOSTER-006/022 pooled analysis, similar demographic characteristics were observed in the HZ/su and Placebo groups (Table 4). More female subjects than male subjects were included in these studies. The mean age of participants at enrolment was 68.6 years for both the HZ/su and Placebo groups. The majority of subjects were white (74.3% and 74.2%, in the HZ/su and Placebo groups, respectively), followed by persons of Asian heritage (18.3% in both groups), persons of other heritage (5.9% and 6.1%, respectively) and persons of African heritage (1.5% and 1.3% respectively).

A total of 2,680 HZ/su subjects and 2,683 Placebo subjects were part of the TVC for North America (which includes subjects from the US and Canada). Similar demographic characteristics were observed in the HZ/su and Placebo groups (Table 4). The mean age of participants at enrolment was 69.3 years and 69.4 years in the HZ/su and Placebo groups, respectively. The majority of subjects were white (93.1% and 93.0%, respectively), followed by persons of African heritage (5.8% and 5.2%, respectively), persons of Asian Heritage (0.6% and 0.9%, respectively) and person of other heritage (0.5% and 0.9%, respectively).

Table 4 ZOSTER-006/022 pooled analysis: Summary of demographic characteristics overall and for North American subjects (TVC, subjects ≥50 YOA)

Demographics	Subjects, n (%)			
	Overall study population		North American subjects	
	HZ/su N=14,645	Placebo N=14,660	HZ/su N=2680	Placebo N=2683
Mean age, years (SD)	68.6 (9.8)	68.6 (9.9)	69.3 (9.7)	69.4 (9.8)
Sex, n (%)				
Male	6147 (42.0)	6113 (41.7)	1146 (42.8)	1097 (40.9)
Female	8498 (58.0)	8547 (58.3)	1534 (57.2)	1586 (59.1)
Race, n (%)				
African	219 (1.5)	196 (1.3)	156 (5.8)	139 (5.2)
Asian	2682 (18.3)	2688 (18.3)	16 (0.6)	24 (0.9)
White	10878 (74.3)	10883 (74.2)	2494 (93.1)	2496 (93.0)
Other	866 (5.9)	893 (6.1)	14 (0.5)	24 (0.9)
Ethnicity, n (%)				
Hispanic	1426 (9.7)	1434 (9.8)	76 (2.8)	75 (2.8)
Non-Hispanic	13219 (90.3)	13226 (90.2)	2604 (97.2)	2608 (97.2)

N = total number of subjects
n/% = number / percentage of subjects in a given category
SD = standard deviation
African = African Heritage / African American
Asian = Central/South Asian Heritage; East Asian Heritage; Japanese Heritage or South East Asian Heritage
White = Caucasian / European Heritage or Arabic / North African Heritage
Other = American Indian or Alaskan Native; Native Hawaiian or Other Pacific Islander or Other (a person with several different heritages

In addition, the baseline medical conditions were balanced between the HZ/su and Placebo groups in both studies. The most frequently reported medical conditions (≥10% of subjects) were:

- hypertension: respectively 41.9% in HZ/su and 41.0% in Placebo groups in ZOSTER-006, and 59.7% and 59.5% in ZOSTER-022
- osteoarthritis: respectively 19.5% and 20.3% in ZOSTER-006, and 31.5% and 30.2% in ZOSTER-022
- diabetes: respectively 14.5% and 14.7% in ZOSTER-006, and 19.5% in each group in ZOSTER-022
- gastroesophageal reflux: respectively 8.5% and 8.2% in ZOSTER-006, and 10.9% and 10.7% in ZOSTER-022

5.2.2. VE Against HZ

5.2.2.1. VE against HZ in subjects ≥50 YOA (primary objective of ZOSTER-006)

The ZOSTER-006 Final Analysis is the primary analysis supporting VE against HZ in adults ≥50 YOA. VE against HZ in adults ≥50 YOA was demonstrated to be 97.2%, with 6 confirmed HZ cases in the HZ/su group and 210 in the Placebo group. The primary objective of ZOSTER-006 was met since the LL of the 95% CI for VE against HZ was observed to be 93.7%, which is above the pre-specified statistical limit of 25%. There was no subject with more than one confirmed HZ episode during the follow-up period. The median follow-up period was 3.1 years. Similar VE against HZ was observed for all age strata and the secondary confirmatory objectives regarding HZ VE in the 50-59 YOA and 60-69 YOA strata were met (LL of the 95% CIs >10%) (Table 5).

Table 5 ZOSTER-006: Vaccine Efficacy Against First or Only Episode of HZ During the Entire Study Period in ≥50 YOA, Overall and by Age Strata (mTVC, Final Analysis)

	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
Age strata	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥50 YOA **	**7344**	**6**	**23297.0**	**0.3**	**7415**	**210**	**23170.5**	**9.1**	**97.2**	**93.7**	**99.0**
50-59 YOA *	3492	3	11161.3	0.3	3525	87	11134.7	7.8	96.6	89.6	99.4
60-69 YOA *	2141	2	7007.9	0.3	2166	75	6952.7	10.8	97.4	90.1	99.7
≥70 YOA**	1711	1	5127.9	0.2	1724	48	5083.0	9.0	97.9	87.9	100

N = number of subjects included in each group; n = number of subjects having at least one HZ confirmed case
T (year) = sum of follow-up period (censored at the first occurrence of a HZ confirmed case) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
*: VE adjusted by region
**: VE adjusted by age strata and region

Of note, an additional statistical analysis (pre-specified in the Statistical Analysis Plan prior to the final analysis) of VE in adults ≥60 YOA was conducted to evaluate VE in the target population covered by the current ACIP recommendation for HZ vaccination, and the VE was shown to be 97.6% (95% CI: 92.7, 99. 6).

Similar VE against HZ was observed between the Final Analysis (primary) and the EOS analysis (secondary). An additional 3 HZ cases were collected in the HZ/su group from Final Analysis to the EOS analysis. At the EOS analysis, VE against HZ in adults ≥50 YOA was demonstrated to be 96.5% (95% CI: 93.2, 98.5), with 9 confirmed HZ cases in the HZ/su group and 254 in the Placebo group.

5.2.2.2. VE against HZ in subjects ≥70 YOA (co-primary objective of the ZOSTER-006/022 pooled analysis)

The analysis of VE against HZ in adults ≥70 YOA was a co-primary objective for the ZOSTER-006/022 pooled analysis and a primary objective for the ZOSTER-022 analysis. VE against HZ in adults ≥70 YOA was a secondary objective in ZOSTER-006.

The ZOSTER-006/022 pooled analysis provides the most accurate VE estimate against HZ in this age group as compared to the VE obtained in the individual studies and is therefore considered as the primary dataset for the ≥70YOA population.

Results on VE against HZ in ≥70 YOA, overall and by age strata (70-79 YOA and ≥80 YOA), from the ZOSTER-006/022 pooled analysis and from ZOSTER-022 are presented in Table 6.

Considering the ZOSTER-006/022 pooled analysis, the overall VE against HZ in adults ≥70 YOA was 91.3%, with 25 confirmed HZ cases in the HZ/su group and 284 in the Placebo group (Table 6). The primary hypothesis for the demonstration of VE against HZ was met, as the observed LL of the 95% CI was 86.9%, which was above the pre-specified statistical criterion of 10%. Similar VE against HZ was observed for the 70-79 YOA and ≥80 YOA strata, i.e., 91.3% and 91.4%, respectively. Note that the ZOSTER-006/ 022 pooled analysis was not powered for HZ VE by age strata, but as a result of the high VE reached across age strata, the LL of the CI was also well above 10% in both the 70-79 YOA and ≥80 YOA strata. The median follow-up period was 4.0 years. Efficacy of HZ/su >91% in the oldest age stratum, in which the incidence and severity of HZ is highest, suggests a significant clinical benefit for subjects in this age population.

Table 6 ZOSTER-006/ 022 pooled analysis: Vaccine efficacy against first or only episode of HZ during the entire study period in adults ≥70 YOA, overall and by age strata (mTVC)

Age strata	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥70YOA **	**8250**	**25**	**30725.5**	**0.8**	**8346**	**284**	**30414.7**	**9.3**	**91.3**	**86.88**	**94.5**
70-79YOA *	6468	19	24410.9	0.8	6554	216	24262.8	8.9	91.3	86.0	94.9
≥80YOA *	1782	6	6314.6	1.0	1792	68	6151.9	11.1	91.4	80.2	97.0

N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000) = Incidence rate of subjects reporting at least one event
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine Efficacy (Poisson method)
*: VE adjusted by region
**: VE adjusted by age strata and region

In the ZOSTER-022 analysis, the overall VE against HZ in adults ≥70 YOA was consistent with the VE estimate obtained in the ZOSTER-006/022 pooled analysis and

the primary objective of ZOSTER-022 was met (LL of the 95% CI >10%). The median follow-up period was 3.9 years.

Section 7.6.2.1 provides more background information on all 9 and 23 HZ breakthrough cases acquired in the HZ/su group of ZOSTER-006 (≥50 YOA, EOS) and ZOSTER-022 (≥70 YOA), respectively.

5.2.2.3. VE against HZ by region

When considering VE against HZ by region (Australia/Asia, Europe, Latin America and North America), similar estimates of VE against HZ between regions were observed in adults ≥50 YOA and ≥70 YOA (Table 7). The results for VE against HZ in all regions were consistent with the overall VE against HZ, i.e., HZ VE point estimates for all regions were within the 95% CI of the overall VE estimate for the respective analyses.

HZ/su had an overall VE of 95.7% (95% CI: 83.7, 100.0) and 90.1% (95% CI: 77.0, 96.5) in preventing HZ in North American subjects ≥50 YOA (ZOSTER-006 EOS analysis) and ≥70 YOA (ZOSTER-006/ 022 pooled analysis) respectively, compared to the Placebo group. The overall VE against HZ in North American subjects ≥70 YOA in ZOSTER-022 was 87.3%, which is consistent with the results obtained in the ZOSTER-006/ 022 pooled analysis.

Table 7 ZOSTER-006 and ZOSTER-006/ZOSTER-022 pooled analyses: Vaccine efficacy against first or only episode of HZ during the entire study period by region in adults ≥50 YOA and ≥70 YOA (mTVC)

Region	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥50 YOA (ZOSTER-006)											
Australia/Asia *	1555	3	6318.3	0.5	1574	76	6183.5	12.3	**96.1**	88.2	99.3
Europe *	3785	3	14986.9	0.2	3828	105	14878.7	7.1	**97.2**	91.4	99.5
Latin America *	709	1	2560.2	0.4	724	27	2597.0	10.4	**96.3**	77.2	100.0
North America *	1291	2	4852.4	0.4	1287	46	4800.3	9.6	**95.7**	83.7	100.0
≥70 YOA (ZOSTER-006/ZOSTER-022 pooled analysis)											
Australia/Asia *	1526	4	5799.2	0.7	1559	81	5735.2	14.1	**95.1**	87.0	98.7
Europe *	4501	12	17038.4	0.7	4543	120	16898.0	7.1	**90.1**	82.0	95.1
Latin America *	597	3	2052.6	1.5	613	24	2076.4	11.6	**87.3**	58.1	97.6
North America *	1626	6	5835.3	1.0	1631	59	5705.1	10.3	**90.1**	77.0	96.5

N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
* : VE adjusted by age strata

5.2.2.4. VE against HZ by gender, race and ethnicity

When considering VE against HZ by gender, similar estimates of VE against HZ between genders were observed in adults ≥50 YOA and ≥70 YOA (Table 8). The results for VE against HZ by gender were consistent with the overall VE against HZ, i.e., HZ VE point estimates for males and females were within the 95% CI of the overall VE estimate for the respective analyses.

By race (Table 9), the VE for subjects ≥70 YOA of Asian, White and Other heritages was consistent to the overall VE in subjects ≥70 YOA (i.e. the point estimates of VE by race were within the 95% CI of the overall VE estimate in subjects ≥70 YOA). For subjects ≥70 YOA of African heritage, the sample size was small (approximately 80 subjects in each group) and as a consequence the number of HZ cases was insufficient to allow for the calculation of VE against HZ in this subgroup.

By ethnicity (Table 10), similar estimates of VE against HZ between subjects of Hispanic and non-Hispanic ethnicities were observed in adults ≥70 YOA. The results for VE against HZ by ethnicity were consistent with the overall VE against HZ, i.e., HZ VE point estimates for Hispanic and non-Hispanic subjects were within the 95% CI of the overall VE estimate for subjects ≥70 YOA in the ZOSTER-006/022 pooled analysis.

Table 8 ZOSTER-006 and ZOSTER-006/ZOSTER-022 pooled analysis: Vaccine efficacy against first or only episode of HZ during the entire study period by gender in adults ≥50 YOA and ≥70 YOA (mTVC)

Gender	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥50 YOA (ZOSTER-006)											
Male*	2860	4	11096.8	0.4	2871	86	10886.6	7.9	**95.4**	87.8	98.8
Female*	4480	5	17621.0	0.3	4542	168	17572.8	9.6	**97.0**	92.9	99.1
≥70 YOA (ZOSTER-006/ZOSTER-022 pooled analysis)											
Male*	3736	10	13827.5	0.7	3753	123	13597.4	9.0	**92.0**	84.7	96.3
Female*	4514	15	16898.0	0.9	4593	161	16817.3	9.6	**90.7**	84.2	95.0

N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
* : VE adjusted by age strata and region

Table 9 ZOSTER-006/ZOSTER-022 pooled analysis: Vaccine efficacy against first or only episode of HZ during the entire study period, by race in adults ≥70 YOA (mTVC)

Race	HZ/su				Placebo				Vaccine Efficacy		
									%	95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)		LL	UL
African*	85	0	289.0	0.0	81	1	272.2	3.7	**100.0**	<0	100.0
Asian*	1410	4	5343.3	0.7	1434	79	5277.2	15.0	**95.0**	86.6	98.7
White*	6423	20	23936.2	0.8	6475	190	23645.1	8.0	**89.6**	83.5	93.8
Other*	332	1	1157.0	0.9	356	14	1220.1	11.5	**92.6**	51.2	99.8

African = African Heritage / African American
Asian = Central/South Asian Heritage; East Asian Heritage; Japanese Heritage or South East Asian Heritage
White = Caucasian / European Heritage or Arabic / North African Heritage
Other = American Indian or Alaskan Native; Native Hawaiian or Other Pacific Islander or Other (a person with several different heritages
N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method)
* : VE adjusted by age strata and region

Table 10 ZOSTER-006/ZOSTER-022 pooled analysis: Vaccine efficacy against first or only episode of HZ during the entire study period, by ethnicity in adults ≥70 YOA (mTVC)

Ethnicity	HZ/su				Placebo				Vaccine Efficacy		
									%	95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)		LL	UL
Hispanic*	648	3	2231.4	1.3	655	26	2224.5	11.7	**88.1**	61.2	97.7
Not Hispanic*	7602	22	28494.1	0.8	7691	258	28190.1	9.2	**91.6**	86.9	94.8

Hispanic = American Hispanic or Latino
Not Hispanic = Not American Hispanic or Latino
N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
LL, UL = 95% Lower and Upper confidence limits; VE (%) = Vaccine Efficacy (Poisson method)
* : VE adjusted by age strata and region

5.2.2.5. VE against HZ over time

The sufficiently long follow-up of studies ZOSTER-006 and ZOSTER-022 allowed for the evaluation of the VE against HZ over successive yearly follow-up (FU) periods. This sensitivity analysis was performed up to 4 years after vaccination (median follow-up is 4.1 years in ZOSTER-006 and 3.9 years in ZOSTER-022).

Analysis of VE against HZ over time as performed at ZOSTER-006 EOS in ≥50 YOA and on pooled ZOSTER-006 and ZOSTER-022 data in ≥70 YOA is presented in Table 11.

In both age strata, VE remained high up to the 4th year after vaccination (currently available data), i.e., 98.4% during the first year and 93.1% during the 4th year in adults ≥50 YOA, and 97.6% during the 1st year and 87.9% during the 4th year in adults ≥70 YOA.

Table 11 ZOSTER-006 and ZOSTER-006/ZOSTER-022 pooled analysis: Vaccine efficacy against first or only episode of HZ during the entire study period by time in adults ≥50 YOA and ≥70 YOA (mTVC)

Time	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥50 YOA (ZOSTER-006)											
Year 1 *	7340	1	7279.8	0.1	7413	62	7312.1	8.5	**98.4**	90.6	100.0
Year 2 *	7190	4	7134.6	0.6	7192	68	7092.1	9.6	**94.2**	84.3	98.5
Year 3 *	7048	0	6972.6	0.0	6998	68	6891.0	9.9	**100.0**	94.5	100.0
Year 4 *	6859	4	7330.8	0.5	6741	56	7164.2	7.8	**93.1**	81.2	98.2
≥70 YOA (ZOSTER-006/ZOSTER-022 pooled analysis)											
Year 1*	8250	2	8156.2	0.2	8346	83	8206.2	10.1	**97.6**	90.9	99.7
Year 2*	8039	7	7916.9	0.9	8024	87	7860.5	11.1	**92.0**	82.8	96.9
Year 3*	7736	9	7612.2	1.2	7661	58	7488.4	7.7	**84.7**	69.0	93.4
Year 4*	7426	7	7040.3	1.0	7267	56	6859.6	8.2	**87.9**	73.3	95.3

N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
*VE adjusted by age strata and region
Year 1: From 30 days after second vaccination to 395 days after second vaccination
Year 2: From >395 days after second vaccination to 760 days after second vaccination
Year 3: From >760 days after second vaccination to 1125 days after second vaccination
Year 4: From >1125 days after second vaccination until last contact date

5.2.3. VE Against PHN

5.2.3.1. VE against PHN in adults ≥70 YOA (co-primary objective of the ZOSTER-006/022 pooled analysis)

Estimation of the VE against overall PHN in adults ≥70 YOA was a co-primary objective of the ZOSTER-006/022 pooled analysis. The results of this analysis are presented in Table 12.

Overall, VE against PHN in adults ≥70 YOA was 88.8%, with 4 PHN cases in the HZ/su group and 36 in the Placebo group; thus the co-primary objective of the ZOSTER-006/ 022 pooled analysis was met (LL of the 95% CI >0%) as the observed LL of the 95% CI was 68.7%. A similar VE against PHN was observed in the 70-79 YOA stratum, i.e., VE was 93.0% (95% CI: 72.4, 99.2), with 2 PHN cases in the HZ/su group and 29 in the Placebo group. Note that pooled analysis was not powered for PHN VE by age strata, but as a result of the high VE against PHN achieved in this age stratum, the LL of the 95% CI was also above 0%. In the ≥80 YOA stratum, VE against PHN was 71.2%, however, the LL of the 95% CI was <0% due to the low number of PHN cases, i.e., 2 PHN cases in the HZ/su group and 7 in the Placebo group.

Table 12 ZOSTER-006/ZOSTER-022 pooled analysis and ZOSTER-022: Vaccine efficacy against first or only episode of PHN during the entire study period in adults ≥70 YOA and by age strata (mTVC)

Age strata	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
Pooled ZOSTER-006/022											
≥70YOA **	8250	4	30760.3	0.1	8346	36	30942.0	1.2	88.8	68.7	97.1
70-79YOA *	6468	2	24438.8	0.1	6554	29	24660.4	1.2	93.0	72.4	99.2
≥80YOA *	1782	2	6321.5	0.3	1792	7	6281.6	1.1	71.2	<0	97.1

N = number of subjects included in each group; n = number of subjects having at least one PHN
T (year) = sum of follow-up period (censored at the first occurrence of PHN) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
* : VE adjusted by region
** : VE adjusted by age strata and region

5.2.3.2. VE against PHN in adults ≥50 YOA (secondary objective of ZOSTER-006)

VE against PHN in adults ≥50 YOA was a secondary objective of ZOSTER-006. Overall, VE against PHN in adults ≥50 YOA was 100%, with no PHN cases in the HZ/su group and 18 in the Placebo group (Table 13). Therefore, this secondary objective of ZOSTER-006 was met (LL of the 95% CI >0%).

ZOSTER-006 was not powered for analysis of PHN VE by age strata, but as a result of the 100% VE against PHN reached in each age stratum, the LL of the 95% CI was also above 0% in the 50-59 YOA and ≥70 YOA strata. However, as there were only 2 reported cases of PHN in the Placebo group in the 60-69 YOA stratum, VE against PHN was not significant in this age stratum.

Table 13 ZOSTER-006: Vaccine efficacy against first or only episode of PHN during the entire study period in adults ≥50 YOA and by age strata (mTVC – EOS analysis)

Age strata	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
≥50 YOA **	7340	0	28734.6	0.0	7413	18	28943.7	0.6	100.0	77.1	100.0
50-59 YOA *	3491	0	13789.7	0.0	3523	8	13928.7	0.6	100.0	40.8	100.0
60-69 YOA *	2140	0	8621.4	0.0	2166	2	8674.4	0.2	100.0	<0	100.0
≥70 YOA**	1709	0	6323.4	0.0	1724	8	6340.6	1.3	100.0	41.4	100.0

N = number of subjects included in each group; n = number of subjects having at least one PHN
T (year) = sum of follow-up period (censored at the first occurrence of PHN) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
* : VE adjusted by region
** : VE adjusted by age strata and region

5.2.3.3. VE against PHN by region

By region, the VE against PHN in subjects ≥70 YOA for Australia/Asia, Europe and North America was 90.8 % (95%CI: 36.4, 99.8), 86.8 % (95%CI: 42.2, 98.6) and 100.0 % (95%CI: 31.2, 100.0), respectively. The VE against PHN for Latin America had a LL of the 95% CI that was <0% due to the low number of PHN cases accrued.

5.2.3.4. VE against PHN by gender, race and ethnicity

The results of the analyses of VE against PHN by gender, race, ethnicity and region for the mTVC of the ZOSTER-006/022 pooled analysis are presented in Table 14. These studies were not designed or powered for these sub-group analyses. The incidence of PHN is low in the overall study population and the VE against PHN in these analyses have large uncertainty ranges; especially when considering smaller subpopulations. For the subgroups where a sufficient number of PHN cases could be accrued, consistently high VE against PHN were observed similar to the VE against PHN in all subjects ≥70 YOA.

Table 14 ZOSTER-006/022 pooled analysis: Vaccine efficacy against first or only episode of PHN during the entire study period by gender, race and ethnicity in adults ≥70 YOA (mTVC)

Gender	HZ/su				Placebo				Vaccine Efficacy		
										95% CI	
	N	n	T(year)	n/T (per 1000)	N	n	T(year)	n/T (per 1000)	%	LL	UL
Gender											
Male*	3736	2	13837.7	0.1	3753	12	13831.4	0.9	**83.3**	24.8	98.2
Female*	4514	2	16922.6	0.1	4593	24	17110.6	1.4	**91.5**	65.7	99.1
Race											
African*	85	0	289.0	0.0	81	0	273.2	0.0	**-**	-	-
Asian*	1410	1	5350.7	0.2	1434	10	5434.4	1.8	**89.8**	28.5	99.8
White*	6423	3	23962.3	0.1	6475	24	23991.8	1.0	**87.5**	58.7	97.6
Other*	332	0	1158.3	0.0	356	2	1242.6	1.6	**100.0**	<0	100.0
Ethnicity											
Hispanic*	648	1	2234.6	0.4	655	3	2269.6	1.3	**65.9**	<0	99.4
Not Hispanic*	7602	3	28525.7	0.1	7691	33	28672.4	1.2	**90.9**	70.8	98.2

African = African Heritage / African American
Asian = Central/South Asian Heritage; East Asian Heritage; Japanese Heritage or South East Asian Heritage
White = Caucasian / European Heritage or Arabic / North African Heritage
Other = American Indian or Alaskan Native; Native Hawaiian or Other Pacific Islander or Other (a person with several different heritages
Hispanic = American Hispanic or Latino
Not Hispanic = Not American Hispanic or Latino
N = number of subjects included in each group; n = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode) expressed in years
n/T (per 1000)= Incidence rate of subjects reporting at least one event
VE (%) = Vaccine Efficacy (Poisson method); LL, UL = 95% Lower and Upper confidence limits
* : VE adjusted by age strata

5.2.4. Other Vaccine Efficacy Objectives

Other secondary efficacy objectives were evaluated in subjects with confirmed HZ in the individual ZOSTER-006 and ZOSTER-022 studies; these include VE in reducing (i) HZ-related mortality and hospitalizations; (ii) incidence of HZ-associated complications [other than PHN], (iii) use and duration of use of pain medications for HZ, (iv) duration of HZ-associated pain rated 3 or greater on the ZBPI. As a consequence of the high VE against HZ, a low number of breakthrough cases were accrued, and therefore it was not possible to draw firm conclusions on some of these secondary objectives. VE against PHN was also estimated in subjects ≥50 YOA with a confirmed case of HZ (secondary objective in the ZOSTER-006/022 pooled analysis).

No HZ-related fatal cases were reported in ZOSTER-006 and ZOSTER-022 and there were 5 HZ-related hospitalizations reported in the Placebo group in ZOSTER-022. Only a few HZ complications were reported: no cases in the HZ/su group in ZOSTER-006 and

one case of ophthalmic disease in the HZ/su group in ZOSTER-022 compared to 6 and 10 HZ-related complications in the Placebo groups of ZOSTER-006 and ZOSTER-022, respectively.

In view of the unexpectedly high efficacy of the vaccine, GSK decided to perform an additional *post-hoc* analysis to evaluate the overall VE in preventing HZ-associated complications (other than PHN), similar to the analysis performed on overall PHN VE. The analysis was performed on the ZOSTER-006/022 pooled efficacy data in order to have the most robust output by increasing the sample size of this analysis. When considering all adults ≥50 YOA (N = 27,916), VE was 93.7% (95% CI: 59.5, 99.9), with one case in the HZ/su group versus (vs.) 16 cases in the Placebo group. When considering all adults ≥70 YOA (N = 16,596), VE was 91.6% (95% CI: 43.4, 99.8), with one case in the HZ/su group vs. 12 cases in the Placebo group.

The VE in reducing the use of pain medication in adults ≥70 YOA with confirmed HZ in ZOSTER-022was 39.6% (95% CI: 10.7, 64.8), with 43.5% of subjects in the HZ/su group and 71.8% of subjects in the Placebo group having taken at least one pain medication for HZ. VE in terms of reduction of duration of pain medication associated with HZ was 49.3% (95% CI: 2.9, 73.5), with a median duration of pain medication of 30 days in the HZ/su group and 38 days in the Placebo group. Note that in ZOSTER-006, no significant reduction of use and duration of pain medication similar to the one observed in ZOSTER-022 was observed in any age strata, as a consequence of the high HZ VE and subsequently low number of HZ cases in the HZ/su group.

The duration of HZ-associated pain rated 3 or greater on the ZBPI was evaluated as a secondary objective in ZOSTER-006, ZOSTER-022, and the ZOSTER-006/ZOSTER-022 pooled analysis. Due to the high VE against HZ, the studies lacked statistical power to demonstrate efficacy in terms of reduction in duration of HZ-associated pain rated 3 or greater on the ZBPI. However, when considering the descriptive statistics of the mean duration of HZ-associated pain with a score greater than 3 in number of days, there was a trend for a shorter duration in the HZ/su group vs. Placebo group in all analyses, i.e., 20.6 vs. 30.2 days in adults ≥50 YOA in ZOSTER-006, 34.6 vs. 48.5 days in adults ≥70 YOA in ZOSTER-022, and 32.1 vs. 47.5 days in adults ≥70 YOA in the ZOSTER-006/022 pooled analysis.

Under the assumption that HZ/su would be efficacious against HZ, demonstrating VE against PHN in subjects ≥50 YOA with a confirmed case of would have required a prohibitively large sample size in adults ≥50 YOA. Therefore, the analysis of PHN prevention in subjects with confirmed HZ was not adequately powered. In the overall mTVC of the pooled analysis in ≥50 YOA, 4/32 (12.5%) subjects with confirmed HZ in the HZ/su group developed PHN and 46/477 (9.6%) subjects with a confirmed HZ in the Placebo group developed PHN. Considering this subset of subjects with confirmed HZ cases, VE against PHN was 0.29% (95% CI: <0, 65.6). As expected, VE against PHN in this subset could not be shown.

5.2.5. Conclusions Regarding Vaccine Efficacy of HZ/su

In both efficacy studies and in the ZOSTER-006/022 pooled analysis, all primary and secondary objectives with pre-specified criteria were successfully met. The efficacy results of the pivotal Phase III studies ZOSTER-006 and ZOSTER-022 support the proposed indication of the prevention of HZ in adults ≥50 YOA. The results also support the statement that by preventing HZ, HZ/su reduces the overall incidence of PHN.

The VE against HZ was 97.2% in adults ≥50 YOA (ZOSTER-006) and 91.3% in adults ≥70 YOA (ZOSTER-006/022 pooled analysis). The data also show that the VE across all age strata are consistently high.

High VE against HZ was maintained up to the fourth year post vaccination (the last timepoint currently assessed) in adults ≥50 YOA (ZOSTER-006) and ≥70 YOA (ZOSTER-006/ 022 pooled analysis). VE against HZ remained high in both studies with a median follow-up time of 3.1 years and 4.1 years in ZOSTER-006 for the final analysis and EOS analysis, respectively, and a median follow-up of 3.9 years in ZOSTER-022. Persistence of efficacy against HZ will be further investigated in ZOSTER-049, which will follow HZ/su recipients from ZOSTER-006 and ZOSTER-022 for at least 10 years after first vaccination.

The co-primary objective to demonstrate the VE of HZ/su against overall PHN in adults ≥70 YOA in the ZOSTER-006/022 pooled analysis was met. The VE against PHN was 88.8% in adults ≥70 YOA.

In the HZ/su group, no cases of PHN occurred in ZOSTER-006, and 4 cases of PHN occurred in ZOSTER-022. VE against PHN was evaluated as a secondary objective in both studies, but the individual studies were not powered for this analysis. Of note, if the success criteria for demonstrating PHN VE in the ZOSTER-006/022 pooled analysis were to be applied for adults ≥50 YOA in ZOSTER-006 and for adults ≥70 YOA in ZOSTER-022, the criteria would be met, reflective of the consistency of the effect against PHN in all age strata.

Due to the high HZ VE, resulting in a low number of HZ cases in the HZ/su group, no conclusions could be drawn regarding most of the specific objectives related to subjects with breakthrough HZ. Consequently, it was not possible to demonstrate VE against breakthrough PHN. However, as HZ is a prerequisite for developing PHN, it is considered that due to the high level of efficacy in prevention of HZ, HZ/su also prevents PHN.

A *post-hoc* analysis to evaluate overall VE against pre-specified HZ-associated complications other than PHN (HZ vasculitis, disseminated disease, ophthalmic disease, neurologic disease, visceral disease, and stroke) on ZOSTER-006/ 022 pooled data in all subjects has shown significant VE in both the ≥50 YOA and ≥70 YOA strata. When considering all adults ≥50 YOA, VE was 93.7%, with one case in the HZ/su group vs. 16 cases in the Placebo group. In all adults ≥70 YOA, VE was 91.6%, with one case in the HZ/su group vs. 12 cases in the Placebo group.

Overall, there was a trend towards less severe HZ-associated pain in subjects vaccinated with HZ/su compared to Placebo. In ZOSTER-022, statistically significant VE in reduction in the use and duration of pain medication for HZ was estimated.

Since ZOSTER-006 and ZOSTER-022 were conducted at 220 study sites in 18 countries globally, the VE estimated from these studies can be considered representative for the global population ≥50 YOA. Furthermore, the eligibility criteria for ZOSTER-006 and ZOSTER-022 permitted recruitment of a broadly representative adult population ≥50 YOA, which allows extrapolation of the results to the general target population.

To summarize, HZ/su demonstrated a VE against HZ of 97.2% in adults ≥50 YOA and of 91.3% in adults ≥70YOA. The VE against PHN was 88.8% in adults ≥70YOA, with no cases of PHN observed in the HZ/su group in ZOSTER-006 and 4 cases observed in the HZ/su group in ZOSTER-022. The high efficacy of HZ/su limited the ability to assess the VE of HZ/su in preventing other complications of HZ in subjects with HZ. In addition, the VE efficacy against HZ persisted for 4 years in both studies without evidence of substantial waning in either age stratum. Hence, HZ/su provides a significant clinical benefit to adults ≥50 YOA which is sustained through all age strata evaluated. The efficacy data support the proposed indication in the Prescribing Information (PI).

6. IMMUNOGENICITY (PHASE III)

The pivotal Phase III efficacy studies, ZOSTER-006 and ZOSTER-022, were focused on the assessment of efficacy against HZ, with supportive immunogenicity data from a subset of subjects from these two studies. Additional Phase III studies were conducted to evaluate product attributes through immunogenicity analyses. These studies included the evaluation of: (i) flexibility in schedule for the administration of the second dose; (ii) the ability to administer HZ/su concomitantly with a seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine; (iii) the administration of HZ/su in subjects with a history of HZ, and (iv) the demonstration of manufacturing consistency through a lot-to-lot consistency study.

HZ/su was designed to induce both CMI and humoral immune responses. CMI objectives were evaluated during the course of the Phase I/II and II development to select the final vaccine formulation (refer to Section 4). Once HZ/su was selected based on the optimal CMI and humoral response as well as an acceptable safety profile, HZ/su immunogenicity was evaluated in terms of CMI in a subset of subjects in ZOSTER-006 only, and more broadly in terms of the humoral immune response as measured by the anti-gE ELISA. Anti-gE ELISA is a validated and robust assay suitable for large-scale use that has shown a positive agreement (i.e. concordance) with the CMI ICS assay in terms of vaccine responders, and also good correlation with a VZV neutralisation assay, which indicates that the antibodies induced by HZ/su have the ability to recognize and interfere with the functionality of the native viral gE glycoprotein. The anti-gE ELISA assay was therefore selected as the primary assay for the phase III studies.

6.1. Key Features of Immunogenicity Evaluations

6.1.1. Overview of Study Design and Study Objectives

In ZOSTER-006 and ZOSTER-022, immunogenicity evaluations were performed in a subset of subjects, i.e., the immunogenicity subset. In ZOSTER-006, 138 subjects, equally distributed between the HZ/su and Placebo groups, were randomly allocated in each country to the immunogenicity subset, except in the 3 countries where CMI samples were collected (the US, Japan, and the Czech Republic). In the countries where CMI samples were collected, 156 subjects were allocated to the immunogenicity subset. In ZOSTER-022, only a humoral immunogenicity subset was defined, with 46 subjects, equally distributed between the HZ/su and Placebo groups, randomly allocated in each country, except in the US and Japan, where 92 subjects were allocated. Humoral responses were evaluated in all subjects of the immunogenicity subset, whereas CMI responses were evaluated in a sub-group of the immunogenicity subset of ZOSTER-006, i.e., the CMI subset. The CMI analyses were performed at designated sites that had access to a PBMC processing facility.

The evaluation of immunogenicity in terms of the anti-gE Ab concentrations was a primary objective in the following additional clinical studies:

- **ZOSTER-026**: comparison of different 2-dose schedules: 0, 2-months versus 0, 6- or 0, 12-month in terms of anti-gE Ab concentrations.
- **ZOSTER-004**: co-administration study of HZ/su with seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine, FLU-D-QIV, or *Fluarix*, in terms of anti-gE Ab concentrations and HI titers.
- **ZOSTER-033**: immunogenicity and safety study of subjects with a history of HZ, in terms of anti-gE Ab concentrations.
- **ZOSTER-007**: a lot-to-lot consistency study comparing the consistency in terms of humoral immune response between clinical consistency manufacturing lots.

In addition, the long-term persistence of humoral and CMI responses was assessed in **ZOSTER-024**, a follow-up study of the phase II ZOSTER-003 study.

In all studies, blood sampling for humoral and CMI immunogenicity testing was performed one month after the receipt of the second dose. Details of the humoral and CMI tests used can be found in Section 3.3.

6.1.2. Study Cohorts

In all studies, except ZOSTER-024, the primary analysis of immunogenicity was based on the According-To-Protocol (ATP) cohort for immunogenicity, which included all evaluable subjects from the ATP cohort for analysis of safety (i.e., those meeting all eligibility criteria, complying with the procedures and intervals allowed for the analysis, with no elimination criteria during the study) for whom data concerning immunogenicity endpoint measures were available. In ZOSTER-024, the Total cohort for persistence for analysis of immunogenicity included all vaccinated subjects, in the vaccination phase

(ZOSTER-003) who attended the persistence visit, for whom data concerning immunogenicity endpoint measures were available.

6.1.3. Analysis of Immunogenicity

6.1.4. Inferential analysis

6.1.4.1. Determination of Vaccine Response Rate

Vaccine Response in terms of humoral immunity, was defined as a 4-fold increase in Ab concentrations between the pre- and post-vaccination timepoints in initially seropositive subjects, and a 4-fold increase above the assay cut-off in initially seronegative subjects. The Vaccine Response Rate (VRR) was defined as the number of subjects meeting the definition of a vaccine response over the total number of subjects with immunogenicity data available at the pre- and post-vaccination timepoints. Determination of the VRR in terms of anti-gE Abs was performed as (co)-primary objectives in the following studies: ZOSTER-004 (with and without co-administration with FLU-D-QIV), ZOSTER-026 (different vaccination schedules) and ZOSTER-033 (subjects with a history of HZ).

The objective related to VRR in terms of anti-gE Abs was met if the LL of the protocol-specified CI of VRR in terms of anti-gE Abs was ≥60%. Based on phase II data, the vaccine response assumed in older adults is 95%.

6.1.4.2. Non-inferiority analysis

Non-inferiority analyses in terms of anti-gE Abs were performed in ZOSTER-004 (with and without co-administration with FLU-D-QIV) and ZOSTER-026 (different vaccination schedules), using a likelihood-based Analysis of Covariance (ANCOVA) model; non-inferiority was demonstrated if the UL of the protocol-specified CI for the ELISA geometric mean concentration (GMC) ratio between the control group over the investigational group was below 1.5.

In ZOSTER-004, non-inferiority with regard to the immune response to the 4 strains in the quadrivalent FLU-D-QIV vaccine was demonstrated if, for each strain, the UL of 2-sided 95% CI of the ratio of the Geometric Mean Titers (GMTs) for HI Abs between the Control and the Co-Ad group was below 1.5 (primary objective).

6.1.4.3. Multiple comparisons between groups

In ZOSTER-007 (lot-to-lot consistency study), the 3 lots were considered consistent when the 2-sided 95 % CI of the anti-gE ELISA GMC ratio between all pairs of lots were within [0.67, 1.5] one month post Dose 2, and the 2-sided 95% CI of the VRR differences between each pair of vaccine lot was within [-10%; +10%] at one month post Dose 2.

6.2. ZOSTER-006 and ZOSTER-022: Immunogenicity Results

6.2.1. Descriptive analysis of humoral responses to gE (ZOSTER-006 and ZOSTER-022)

A total of 2,137 and 799 subjects from ZOSTER-006 and ZOSTER-022, respectively, were part of the ATP cohort for immunogenicity, and were evaluated for anti-gE Ab concentrations. Of these subjects, 1,070 and 387 were in the HZ/su groups of ZOSTER-006 and ZOSTER-022, respectively.

In the immunogenicity subset of adults ≥50 YOA in ZOSTER-006, the results showed that one month after the second dose, HZ/su elicited anti-gE Ab GMCs of 52,377 mIU/mL, anti-gE Ab levels were 41.9-fold higher than those at pre-vaccination, and VRR was 98.5% (Table 15, Month 3).

In adults ≥70 YOA from the ZOSTER-006/022 pooled analysis, the results showed that one month after the second dose, HZ/su elicited anti-gE Ab GMCs of 49,692 mIU/mL, anti-gE Ab levels were 34.3-fold higher than those at pre-vaccination, and VRR was 96.6% (Table 15, Month 3).

6.2.2. Descriptive analysis of CMI responses to gE (ZOSTER-006)

In ZOSTER-006, the gE-specific CMI responses were evaluated in a subset of the immunogenicity cohort. Of a total of 430 subjects evaluated in the CMI subset, 212 subjects were vaccinated with HZ/su and were enrolled in 3 countries: the US, Czech Republic and Japan.

In adults ≥50 YOA, median frequencies of gE-specific CMI responses as measured with the ICS test one month after the second dose were 24.6-fold higher than those at pre-vaccination and the median frequency of gE-specific CD4[2+] T-cells was 1,844.1 per million T-cells (Table 16, Month 3). In adults ≥70 YOA, median frequencies of gE-specific CMI responses one month after the second dose were 33.2-fold higher than those at pre-vaccination and the median frequency of gE-specific CD4[2+] T-cells was 1,494.6 per million T-cells (Table 16, Month 3).

6.3. Persistence of HZ/su Immune Response

Several studies evaluated the persistence of the immune response to a two-dose schedule of HZ/su administered at 0, 2 months during follow-up periods of more than 1 year, i.e., ZOSTER-006 and ZOSTER-022 up to 3 years after the second dose and ZOSTER-024 up to 6 years after initial vaccination.

6.3.1. ZOSTER-006 and ZOSTER-022

In ZOSTER-006 and ZOSTER-022, immunogenicity was evaluated up to 3 years after the second dose, with 967 evaluable subjects ≥50 YOA in the HZ/su group in ZOSTER-006 (152 subjects in the CMI subset) and 648 evaluable subjects ≥70 YOA in the HZ/su group in the ZOSTER-006/ZOSTER-022 pooled analysis when considering the ATP

cohort for immunogenicity. Anti-gE ELISA responses in both ≥50 YOA and ≥70 YOA as well as gE-specific CD4[2+] T-cell responses in ≥50YOA persisted up to 3 years post last vaccination.

The gE-specific humoral response remained respectively 9.3-fold and 7.2-fold above the baseline pre-vaccination immune response levels through year 3 in subjects ≥50 YOA (ZOSTER-006) and ≥70 YOA (ZOSTER-006/ 022 pooled analysis), respectively (Table 15, Month 38).

CMI was assessed in ZOSTER-006 only. The gE-specific CMI response remained 7.9-fold and 7.3-fold above the baseline pre-vaccination through year 3 in the ≥50 YOA group and the ≥70 YOA group, respectively (Table 16, Month 38).

Table 15 ZOSTER-006 and Pooled ZOSTER-006 and ZOSTER-022 Analyses: Anti-gE Antibody Responses to HZ/su One Month post Dose 2 (at Month 3) and 3 Years post Dose 2 (at Month 38), Overall and ≥70 YOA (humoral subset of ATP cohort for immunogenicity)

Age group[1] (years)	Month 3				Month 38		
	N	VRR % (95% CI)	anti-gE Abs GMC (mIU/ml) (95% CI)	Median fold increase vs. pre-vaccination (Q1, Q3)	N	anti-gE Abs GMC (mIU/ml) (95% CI)	Median fold increase vs. pre-vaccination (Q1, Q3)
≥50 YOA	1,070	98.5 (97.6, 99.1)	52,376.6 (50,264.1, 54,577.9)	41.9 (20.8 to 86.9)	967	11,919.6 (11,345.6, 12,522.7)	9.3 (4.9 to 19.5)
≥70 YOA	742	96.6 (95.1, 97.8)	49,691.5 (47,250.8, 52,258.2)	34.3 (16.7 to 68.5)	648	10,507.7 (9,899.2, 11,153.6)	7.2 (3.5 to 14.5)

N = Number of subjects with available results (for the GMC); VRR = Vaccine Response Rate; GMC = Geometric Mean Concentration;
95% CI = 95% Confidence Interval; Q1, Q3 = First and third quartiles;
[1] ≥50 YOA: ZOSTER-006 analysis; ≥70 YOA: ZOSTER-006/ZOSTER-022 pooled analysis

Table 16 ZOSTER-006: gE-specific CD4[2+] T-cell responses one month post Dose 2 (Month 3) and 3 years post Dose 2 (Month 38) elicited by HZ/su, overall and in adults ≥70 YOA (CMI subset of ATP cohort for immunogenicity)

Age group (years)	Month 3			Month 38		
	N	Median frequency per million T-cells (Q1, Q3)	Median fold increase in frequency vs. pre-vaccination (Q1, Q3)	N	Median frequency per million T-cells (Q1, Q3)	Median fold increase in frequency vs. pre-vaccination (Q1, Q3)
≥50 YOA	164	1,844.1 (1,253.6 to 2,932.3)	24.6 (9.9 to 744.2)	152	738.9 (355.7 to 1,206.5)	7.9 (2.7 to 31.6)
≥70 YOA	52	1,494.6 (922.9 to 2,067.1)	33.2 (10.0 to 1,052.0)	46	480.2 (196.1 to 972.4)	7.3 (1.7 to 31.6)

Q1, Q3 = First and third quartiles; N = Number of subjects with available results

6.3.2. ZOSTER-024

ZOSTER-024 was an extension study of phase II study ZOSTER-003 (antigen dose finding study in subjects ≥60 YOA) and evaluated the persistence of gE-specific CMI and humoral immune responses in the HZ/su group up to 6 years (Month 72) after vaccination. Of the 146 subjects from the ZOSTER-003 HZ/su group who were offered participation in ZOSTER-024, 129 subjects consented to enroll in this study and were included in the Total cohort for persistence at Month 72.

In terms of CMI response, the descriptive statistics showed that the median frequency of gE-specific CD4[2+] T-cells was highest at Month 3 and declined to approximately 50% peak frequency by Month 12. The median (Q1; Q3) frequency was 13.7-fold (6.2, 40.2) above pre-vaccination frequencies at Month 3 and declines to 3.8-fold (1.4; 12.9) above pre-vaccination frequencies through Month 72.

In terms of humoral immune responses, the anti-gE antibody GMCs were highest at Month 3 and declined to approximately 35% peak concentrations by Month 12. The median anti-gE Ab concentration was approximately 38-fold above the baseline pre-vaccination median concentration at Month 3 and at maintained at greater than 7-fold above the baseline pre-vaccination median concentration through Month 72).

6.4. Other Phase III Studies: Key Immunogenicity Results

6.4.1. Evaluation of 0, 6 and 0, 12 Month Dosing Schedules (ZOSTER-026)

ZOSTER-026 was an open-label study with 3 parallel groups randomized in a 1:1:1 ratio, representing the 3 different schedules, designed to evaluate the immunogenicity and safety of HZ/su administered within time intervals of 6 and12 months between doses as compared to a 2 month interval. The VRR of subjects receiving HZ/su according to the 0, 6- and 0, 12-month schedules was determined and anti-gE Ab GMCs following these schedules were inferentially compared with the standard 0, 2-month schedule in adults ≥50 YOA.

The study was conducted in the US and Estonia. A total of 354 subjects were enrolled and were stratified by age (50-59 YOA, 60-69 YOA and ≥70 YOA). Subjects received HZ/su according to one of the following two-dose schedules: 0, 2 month (control; N=119), 0, 6 month (N=119), and 0, 12 month (N=116). A total of 349 subjects completed the study up to one month post last dose.

The co-primary objectives were to be evaluated sequentially, with pre-defined success criteria for these objectives.

The immunogenicity data one month post Dose 2 demonstrated that:

- The primary objective in terms of minimum VRR was met (LL of the 97.5% CI ≥60%) for both the 0, 6 and 0, 12-month schedules, with similar VRRs in both groups, i.e., 96.5% (97.5% CI: 90.4, 99.2) for the 0, 6 month schedule and 94.5% (97.5% CI: 87.6, 98.3) for the 0, 12 month schedule.
- The non-inferiority criterion in terms of anti-gE GMC ratio (UL of the 97.5% CI <1.5) was met for the 0, 6-month schedule (1.16 [97.5% CI: 0.98, 1.39]) but not for the 0, 12-month schedule (1.19 [97.5% CI: 0.93, 1.53]), where it was marginally exceeded.

The results of ZOSTER-026 support that patients may return anytime within 2 to 6 months after the initial vaccination to complete the HZ/su regimen.

6.4.2. Co-administration with Seasonal Influenza Vaccine (ZOSTER-004)

The Phase III study ZOSTER-004 was an open-label, controlled study with 2 parallel groups in a 1:1 ratio, designed to evaluate the immunogenicity and safety of HZ/su when co-administered with GSK's seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine (*Fluarix*- FLU-D-QIV) in adults ≥50 YOA.

The Co-Ad group received one dose of HZ/su and FLU-D-QIV concomitantly at Month 0 and the second dose of HZ/su at Month 2, and the Control group received FLU-D-QIV and HZ/su sequentially (one dose of FLU-D-QIV at Month 0 followed by 2 doses of HZ/su at Months 2 and 4). The study was conducted in the US, Canada, and Germany, and vaccinated a total of 828 subjects, i.e., 413 subjects in the Co-Ad group and 415 subjects in the Control group, and 811 subjects completed this study up to one month post last dose.

The co-primary objectives were to be evaluated using pre-defined success criteria for these objectives. All co-primary objectives needed to be met in order to consider the co-administration of HZ/su with seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine to be acceptable. Therefore, no adjustment was required for the type I error of each primary comparison.

The VRR (in terms of anti-gE antibodies) following co-administration of HZ/su with FLU-D-QIV was 95.8% (95% CI: 93.3, 97.6). The statistical criterion for non-inferiority was met as the observed LL of 93.3% was above the statistical limit of 60%.

The non-inferiority of HZ/su co-administered with FLU-D-QIV compared to HZ/su administered alone with respect to anti-gE GMCs (pre-defined criterion for non-inferiority of ≤1.5) was demonstrated as the UL of the 95% CI for the GMC ratio for anti-gE antibodies of the Control group over the HZ/su-FLU D-QIV co-administration group was 1.2.

The non-inferiority of FLU-D-QIV (all 4 strains) co-administered with HZ/su compared to FLU-D-QIV administered alone with respect to HI Ab GMTs (pre-defined criterion for non-inferiority of ≤1.5) was demonstrated. The UL of the two-sided 95% CI for the GMT

ratio of the Control group over the HZ/su-FLU D-QIV co-administration group was 1.22 for Flu A/California, 1.17 for Flu A/Texas, 1.20 for Flu B/Brisbane and 1.09 for Flu B/Massachusetts.

Since all primary hypotheses were successfully met, it can be concluded that HZ/su can be co-administered with seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine.

6.4.3. Subjects With Previous HZ (ZOSTER-033)

ZOSTER-033 was a single-arm, open-label study to assess the safety and immunogenicity in terms of anti-gE Ab concentration after 2 doses of HZ/su on a 0, 2 month schedule. The study enrolled 96 adults ≥50 YOA with a history of HZ which had been documented by a physician in the subjects' medical record. The study was conducted in the Canada and the Russian Federation. All subjects received at least one dose of HZ/su and 93 subjects completed the study.

The VRR in terms of anti-gE Ab concentrations (primary objective) was 90.2% (95% CI: 81.7, 95.7), which is above the pre-specified success criterion (LL of the 95% CI of VRR was ≥60%), and which is consistent with what has been observed in other clinical studies where HZ/su was administered to adults in the same age group but with no history of HZ (based upon informal comparison of the data to that generated in other clinical studies of HZ/su).

When comparing VRR based on time since HZ, subjects with previous HZ within 5 years of vaccination had lower VRR (85.2% [95% CI: 72.9, 93.4]) than subjects who had previous HZ 5-9 years prior to vaccination (VRR 100% [95% CI: 80.5, 100]) and ≥10 years prior to vaccination (VRR 100% [95% CI: 71.5, 100]). Subjects who had previous HZ within 5 years of vaccination had higher baseline pre-vaccination anti-gE Abs (3,490 mIU/mL) than subjects who had previous HZ 5-9 years prior to vaccination (1,148 mIU/mL) and ≥10 years (1,187 mIU/mL).

The immune response of HZ/su in adults ≥50 YOA with a medically-documented history of HZ is consistent with what has been observed in adults ≥50 YOA with no history of HZ.

6.4.4. Lot-to-lot Consistency (ZOSTER-007)

ZOSTER-007 was a double-blinded study designed to compare 3 consecutively manufactured lots of HZ/su in terms of immunogenicity (primary objective) and to evaluate the safety of these lots in adults ≥50 YOA. Three lots of HZ/su vaccine were compared in a pairwise fashion.

The study enrolled 651 adults ≥50 YOA who were randomized 1:1:1 to receive 2 doses of 3 different lots of HZ/su on a 0, 2 month schedule. The study was conducted in the US, Canada, and Belgium. All subjects received at least one dose of Lot A, Lot B or Lot C (218, 217, and 216 subjects per group, respectively), and 645 subjects completed the study up to one month post Dose 2.

The lot-to-lotconsistency was demonstrated, since the 95 % CI of the anti-gE Ab GMC ratio between all pairs of lots were all within the pre-sepcified interval of [0.67, 1.5] (primary objective).

Lot-to-lot manufacturing consistency was demonstrated in adults ≥50 YOA. The lots used in this study are representative of the final commercial process, as they have been been demonstrated to comply with the all pre-specified comparability criteria agreed with the FDA.

6.5. Conclusions Regarding Immunogenicity of HZ/su vaccine

The immunogenicity data from the Phase II and Phase III studies support the following conclusions:

- Two doses of HZ/su induced robust CMI and humoral immune responses in adults ≥50 YOA (ZOSTER-006). Post Dose 2 frequencies of gE-specific CMI and humoral responses were respectively 24.6-fold and 41.9-fold above pre-vaccination levels, and post Dose 2 VRR in terms of anti-gE Ab concentrations was 98.5% in adults ≥50 YOA. The CMI and humoral immune responses remained above baseline levels for a follow-up period of 3 years post Dose 2 and were respectively 7.9- and 9.3-fold above pre-vaccination levels in adults ≥50 YOA.
- Two doses of HZ/su induced robust CMI and humoral immune responses in adults ≥70 YOA (ZOSTER-006 and ZOSTER-006/022 pooled analysis respectively). Post Dose 2 frequencies of gE-specific CMI and humoral responses were respectively 33.2-fold and 34.3-fold above pre-vaccination levels, and post Dose 2 VRR in terms of anti-gE Ab concentrations was 96.6% in adults ≥70 YOA. The CMI and humoral immune responses remained above baseline levels for a follow-up period of 3 years post Dose 2 and were respectively 7.3- and 7.2-fold above pre-vaccination levels in adults ≥70 YOA.
- The gE-specific CMI and humoral immune responses remained respectively 3.8-fold and 7.3-fold above the baseline pre-vaccination immune response levels until approximately 6 years after vaccination for adults who were ≥60 YOA at the time of initial vaccination (ZOSTER-024).
- HZ/su can be administered according to a flexible schedule where the second dose can be given between and 2 and 6 months after the first dose (ZOSTER-026).
- HZ/su can be co-administered with quadrivalent seasonal influenza vaccine. No clinically relevant interference in the immune response of either the HZ/su or the quadrivalent seasonal influenza vaccine antigens was observed when the two vaccines were administered concomitantly (ZOSTER-004).
- The immune response in subjects with a history of HZ was comparable to the vaccine-induced immune response seen in other studies conducted in subjects ≥50 YOA without history of HZ (ZOSTER-033).
- Lot-to-lot manufacturing consistency was demonstrated in adults ≥50 YOA (ZOSTER-007).

7. OVERVIEW OF SAFETY

7.1. Key Features of Studies

7.1.1. Evaluation of the Safety of HZ/su

The BLA included safety data from 19 clinical studies available at the time of submission, in which subjects received HZ/su. Of these 19 studies, 17 were conducted in >17,000 adults ≥50 YOA and 2 were conducted in IC adults ≥18 YOA. A detailed description of the studies included in the BLA is provided in Appendix Table 1. Figure 10 presents all studies included in the BLA, along with the overall number of subjects included from each study, for which details are presented below.

In the population of adults ≥50 YOA, safety data with a data lock point (DLP) of 12 October 2015 were pooled from all clinical studies with a similar study design where HZ/su (50 μg gE reconstituted in 0.5 mL $AS01_B$) was administered by the intramuscular route according to a 0, 2-month schedule. The studies included in the safety pooling analyses had to be completed with a safety follow-up of at least 1 year post last vaccination. In addition, subjects could not have received co-administered vaccines. Two types of safety pooling analyses were performed: a main safety pooling analysis and a broader safety pooling analysis.

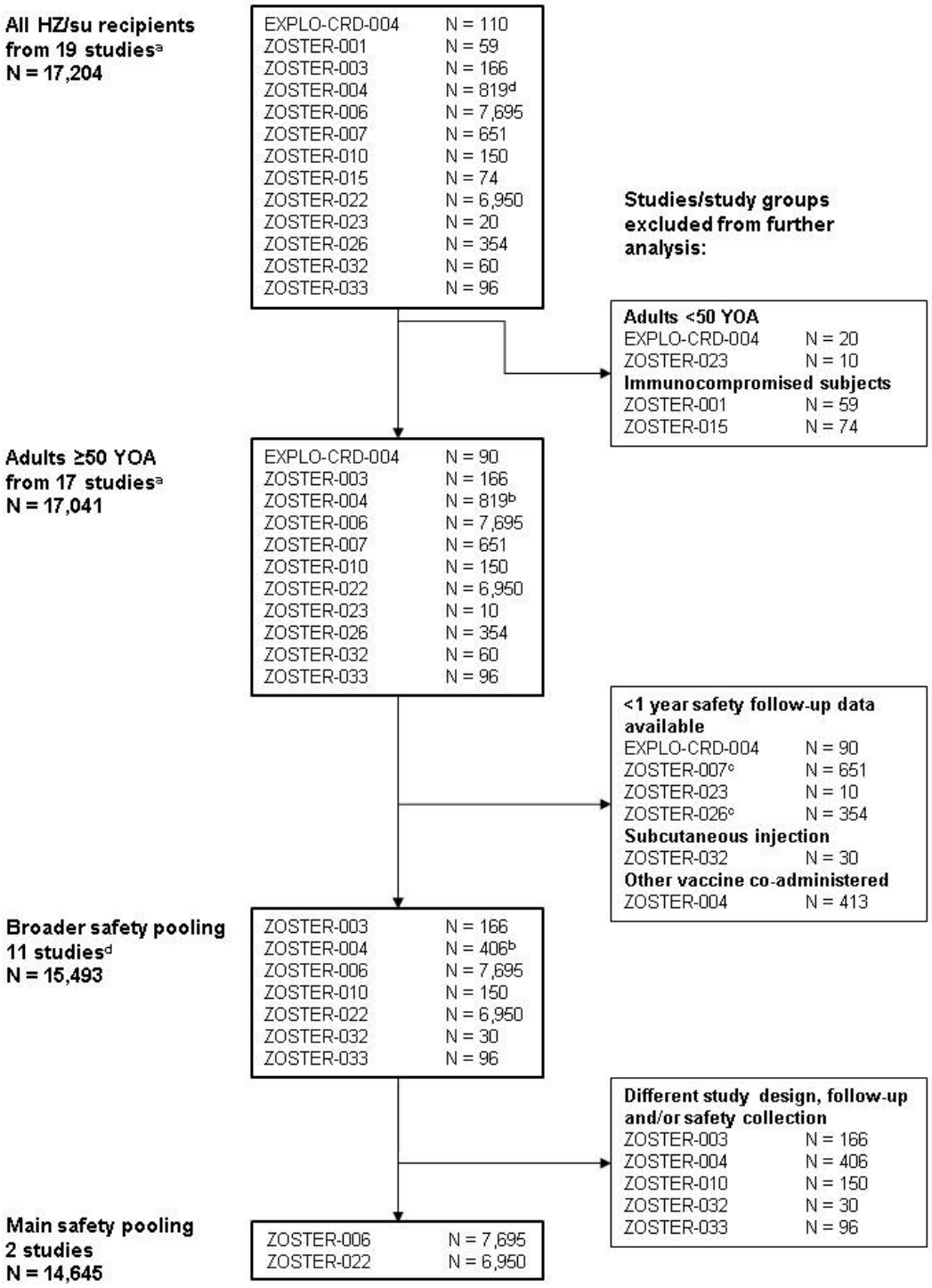
The main safety pooling analysis comprises the safety data from the 2 pivotal Phase III studies ZOSTER-006 and ZOSTER-022, as these studies have a similar study design and were conducted concurrently in the same countries and centers. Because this pooling includes an adequate control group, a comparative analysis was performed on safety data from the HZ/su group versus the Placebo group (saline) in order to assess the RR of reported safety events. The main safety pooling included 29,305 adults ≥50 YOA who received at least one dose of HZ/su (N = 14,645) or Placebo (N = 14,660), which represents >85% of subjects ≥50 YOA who received HZ/su in the overall safety analysis. This main safety pooling is the primary source to identify and estimate frequencies of specific AEs which are included as 'adverse reactions' in the US PI. Therefore, this briefing document mainly presents data from the main safety pooling (Section 7.4).

The **broader safety pooling analysis** is designed to provide additional safety signal detection and evaluation of SAEs, fatalities and pIMDs. This is a descriptive analysis performed on all safety data (except for solicited symtoms) from 11 studies with a safety follow-up period of at least 1 year post last vaccination for the HZ/su group only (N = 15,493; no Placebo comparison). As 94.5% of adults ≥50 YOA and 96.5% of adults ≥70 YOA in the broader safety pooling pertain to ZOSTER-006 and ZOSTER-022, and as the safety conclusions on SAEs, fatalities and pIMDs from the broader safety pooling analysis are consistent with those from the main safety pooling analysis, data from the broader safety pooling are not discussed here.

Section 7.6 summarizes the safety results from **individual studies** not included in the safety pooling analyses because:

- they did not meet the criteria outlined above, i.e., ZOSTER-007 and ZOSTER-026 did not have 1-year safety follow-up data post last vaccination available at the time of the DLP used for the safety pooling, and/or
- they highlighted other safety aspects of HZ/su, i.e., other vaccination schedules in ZOSTER-026, co-administration with another vaccine in ZOSTER-004, subjects with previous HZ in ZOSTER-033, and lot-to-lot consistency in ZOSTER-007.

Figure 10 Diagram on HZ/su exposure in all completed clinical studies included in the BLA (TVC)



[a] These include the 2 exentsion studies from EXPLO-CRD-004 (ZOSTER-018 and -019) and the 4 extension studies of ZOSTER-003 (ZOSTER-011, -012, -013 and -024) all without HZ/su administration.

[b] Although 415 subjects were part of the TVC and received FLU-D-QIV at Dose 1 (see Appendix Table 1), only 406 of them received at least 1 dose of HZ/su at the subsequent doses.

[c] 1-year safety follow-up data post last vaccination were not available at the time of the DLP of the safety pooling.

[a] These include the 4 extension studies from ZOSTER-003 (ZOSTER-011, -012, -013 and -024) without HZ/su administration.

7.1.2. Learnings From Non-clinical Toxicology Testing and Mode of Action Studies

As part of the evaluation of the safety of HZ/su, more than 20 Good Laboratory Practices (GLP) studies in animal models were conducted according to regulatory guidance, including repeat-dose toxicity studies of HZ/su, AS01 or AS01 components, as well as local tolerance, male fertility and reproductive toxicity studies. Collectively, these studies did not reveal any specific concerns that would preclude the use of HZ/su in humans [Destexhe, 2013; Giordano, 2017; Segal, 2015; Segal, 2017]. The main findings of those studies were a dose-dependent cell infiltration at the injection site and transient changes in hematology and clinical chemistry parameters (e.g., temperature, C-reactive protein and albumin/globulin ratio) that were shown to be fully reversed after 4 weeks, all consistent with the mode of action of the adjuvanted vaccine. Repeated administration of the highest tested dose did not reveal any systemic toxicity with no histopathology findings in organs distant from injection sites, such as liver, kidney and brain. No treatment-related changes in liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transpeptidase) were observed. Biodistribution studies in mice confirmed that AS01 components (tagged with radioactive label) were rapidly drained in the lymph node and eliminated through blood, liver and renal or fecal excretion. After 72 hours, 98% of radiolabeled QS-21 was cleared while radiolabeled MPL analogue showed a slower kinetic. Importantly, no significant level of radioactivity in other organs than at the injection site, dLN, kidney and liver were observed. HZ/su or AS01 administered alone in rats showed no effects on fertility, pre- and post-natal development or survival [Segal, 2017]. The gE (100 µg)/$AS01_B$ vaccine formulation, $AS01_B$ and MPL did not produce adverse effects on cardiovascular or respiratory functions in dogs or anesthetized rats [Segal, 2015].

Relevant to the safety assessment, the inflammatory response to AS01 as part of HZ/su has been investigated in various animal models. Investigations revealed that the inflammation induced by AS01 is transient (peak at Day 1 and return to baseline by Day 2-3) at the injection site (muscle) and draining lymph node. The local effect of the adjuvant was further supported by the lack of adjuvant effect on gE administered with AS01 at the same time but at a different site (Figure 11) [Didierlaurent, 2014]. The antigen must be injected at the same injection site and within 24 hours of AS01 administration to observe the adjuvant effect. This suggests that the key elements of the innate immune responses required for AS01 to work are occurring within 24 hours of vaccination. In a non-human primate model, the systemic effect of AS01 was found to be self-limited, with a transient increase in Il-6 and IFN-γ (peak at Day 1) at low levels, suggestive of a spill-over from local activation (Figure 12). An evaluation of blood response in humans confirmed the finding in non-human primates, as the same cytokines were transiently increased in blood of individuals immunized with hepatitis B surface antigen formulated in $AS01_B$ [Burny, 2017]. In particular, no significant changes in the pro-inflammatory cytokines IL-1β or TNF-α were detected.

Figure 11 Requirement for co-localization of gE and AS01 for CMI responses

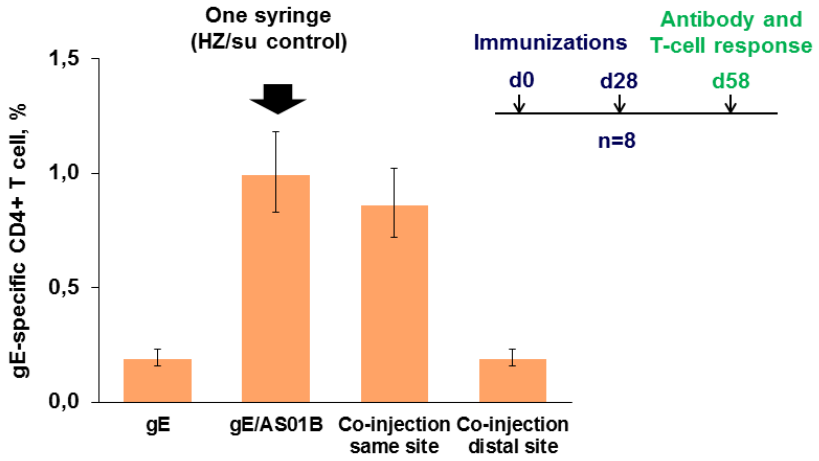
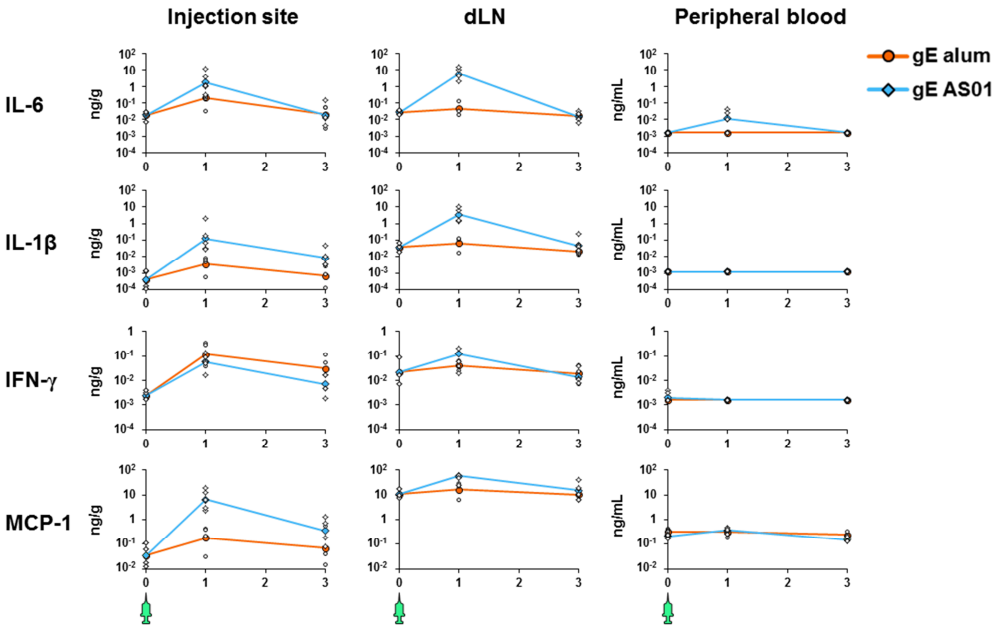


Fig 11: C57BL/6 mice were immunized at days 0 and 28 intramuscularly with gE alone (5 µg) or gE combined with $AS01_B$ (5 µg MPL, 5 µg QS-21) in one syringe (arrow). Two other groups of mice were injected first with $AS01_B$ followed by gE either at the same site ("co-injection, same site") or at the contra-lateral side (i.e. in the other leg, "co-injection distal site"). 30 days after the last immunization, gE-specific CD4+ T cells were monitored in splenocytes as described in Figure 1. Histograms represent geometric means, and error bars represent 95% confidence intervals. [Didierlaurent, 2014]

Figure 12 Local and blood cytokine concentrations after vaccination with HZ/su in rhesus macaques



Chinese rhesus monkeys were vaccinated in the bicep muscle with gE (25 µg) formulated with Aluminum salts (gE/alum; N=6), or AS01 (25µg MPL; 25µg QS-21; gE/AS01; N=7). Cytokine concentrations were measured by multiplex technology, at the indicated time points, in sera and in homogenates of the injection site and draining lymph node (dLN). Baseline values are taken from blood pre-vaccination or from muscle and LN samples unaffected by vaccination. Individual data and geometric means are shown. Data at injection site and in dLN were normalized to tissue weight (ng/g of tissue). All studies were approved by the relevant ethical committee. Reference: poster at Keystone symposium "The Modes of Action of Vaccine Adjuvants", 2014, Seattle.

Overall, the nature and kinetics of the inflammatory profile of AS01 as described in these non-clinical models are consistent with the reactogenicity profile of HZ/su observed in clinical studies. As for any vaccine containing an adjuvant, a theoretical risk of induction/exacerbation of (pre-existing) inflammatory and/or autoimmune conditions cannot be excluded. Considering this and the transient inflammatory profile of AS01 demonstrated in non-clinical experiments, this risk was carefully evaluated in the clinical vaccine safety assessment. As such, specific information on Potential Immune-Mediated Diseases (pIMDs) was collected in all HZ/su clinical studies (see Section 7.2.2).

7.2. Methodology for Safety Assessment

7.2.1. Safety Definitions

The following safety events were collected in the clinical studies with HZ/su:

- Solicited local and general symptoms
- Unsolicited adverse events (AEs), including AEs with medically attended visit
- Serious adverse events (SAEs), including fatal SAEs
- Potential Immune-Mediated Diseases (pIMDs)
- Suspected cases of HZ and HZ complications
- Hypersensitivity including anaphylaxis

Adverse events

Adverse events (AEs) were defined as any untoward medical occurrence in a clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A distinction was made between solicited symptoms and unsolicited AEs.

Solicited symptoms were defined as a group of pre-defined symptoms which are expected to occur with the administered vaccine and were therefore daily recorded by subjects from Day 0 to Day 6 (7-day post-vaccination period) after each vaccination. Solicited local symptoms included pain, redness and swelling at the injection site. Solicited general symptoms included fatigue, gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea and/or abdominal pain), headache, myalgia, shivering and fever (defined as axillary, oral or tympanic temperature ≥37.5°C/99.5°F, or rectal temperature ≥38°C/100.4°F). For most studies, including ZOSTER-006 and ZOSTER-022, temperature was preferentially measured orally. Throughout the development program, the list of solicited symptoms was kept consistent, except for gastrointestinal symptoms which were not recorded in ZOSTER-003, and shivering, which was not recorded in ZOSTER-003 and ZOSTER-010. Of note, these symptoms were only defined as solicited if they occurred during the solicited 7-day post-vaccination period. In addition, in ZOSTER-006 and ZOSTER-022, only a subset of subjects referred to as the 7-day diary

card subset recorded these symptoms as solicited during the 7-day post-vaccination period (see Section 7.2.2 for details).

Unsolicited AEs were defined as any AE reported in addition to those solicited during the clinical study and reported from Day 0 to Day 29 (30-day post-vaccination period) after each vaccination. In contrast to solicited symptoms, there is no pre-defined list of unsolicited AEs to be reported. Symptoms which were 'solicited' during the 7-day post-vaccination period were to be reported as unsolicited AEs if they had an onset outside this 7-day post-vaccination period, or if they were reported by subjects in ZOSTER-006 and ZOSTER-022 who were not part of the 7 day diary card subset (see Section 7.2.2).

For each solicited symptom and unsolicited AE the subject experienced, the subject was asked if he/she received **medical attention** defined as hospitalization, an emergency room visit, or an otherwise unscheduled visit to or from medical personnel for any reason other than routine health care visits.

SAEs

Serious Adverse Events (SAEs) were defined as any untoward medical occurrence that resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity or was a congenital anomaly/birth defect in the offspring of a study subject. This definition was aligned with regulatory requirements. In addition, investigators also had the choice to report additional AEs as SAE when they were considered to be important medical events that did not meet any of the above definitions.

pIMDs

pIMDs are a subset of AEs that include autoimmune diseases and other inflammatory and/or neurological disorders of interest which may or may not have had an autoimmune etiology. pIMDs are AEs of special interest undergoing special safety monitoring for all GSK vaccines containing Adjuvant Systems, including HZ/su. This includes a standardized methodology which has been implemented since 2010 and updated over the past years for the prospective collection of complete and reliable data on pIMDs across clinical studies [Tavares, 2013]. For further details on the methodology, refer to Section 7.2.2.

Suspected cases of HZ and HZ complications

In ZOSTER-006 and ZOSTER-022, suspected cases of HZ were confirmed by PCR or by the HZAC. These confirmed cases were collected, followed and evaluated as primary endpoints for efficacy assessment. In addition, PHN and other pre-specified HZ complications were collected as secondary endpoints for efficacy assessment. In ZOSTER-003 and extension studies, and ZOSTER-010, suspected cases of HZ (whether or not clinically diagnosed by the investigator) were collected throughout the study period as endpoints for safety analyses. In all other studies, suspected cases of HZ and/or HZ-related complications were collected as part of the endpoints for safety analyses and followed the standard AE or SAE reporting process as applicable and as described in

each individual study protocol. No diagnostic procedures to confirm a case of HZ were required.

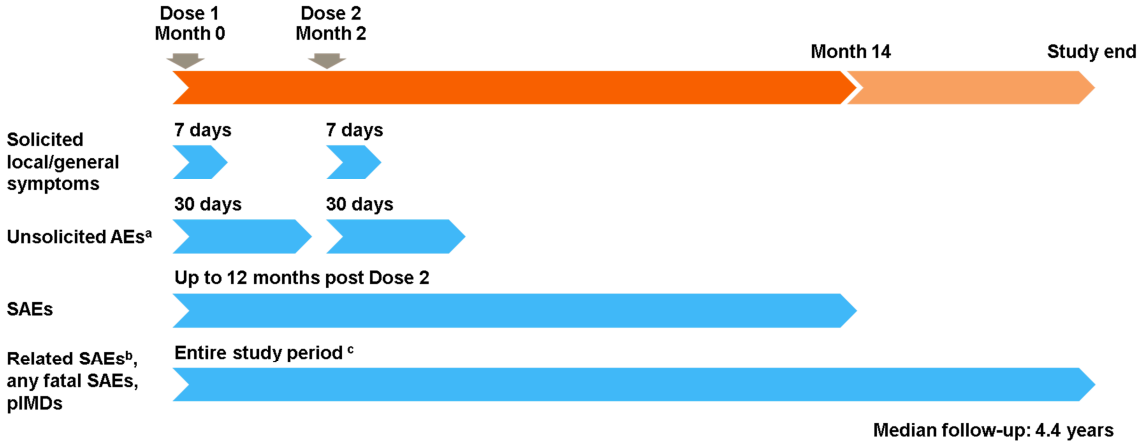
Hypersensitivity including anaphylaxis

As for other vaccines, serious hypersensitivity reactions, including anaphylaxis to one or several components of the vaccine, were considered AEs of special interest. Anaphylaxis is an acute hypersensitivity reaction with multi-organ system involvement that can present as, or rapidly progress to, a severe life-threatening reaction. Anaphylaxis following immunization is serious but rare, estimated to occur in the range of 1 to 10 per 1 million doses distributed, depending on the vaccine studied [Rüggeberg, 2007]. During the Clinical Development Program (CDP) of HZ/su, subjects with known reaction or hypersensitivity to one or several components of the vaccine were excluded from enrolment. Potential cases featuring acute hypersensitivity and/or anaphylaxis were collected as described in Section 7.4.5.3.

7.2.2. Time Periods and Methodology for Detecting, Recording and Evaluating AEs

The information presented in this section mainly pertains to ZOSTER-006 and ZOSTER-022. Safety information from other studies is included when relevant. An overview of the reporting periods for safety data collection in ZOSTER-006 and ZOSTER-022 is presented in Figure 13. The median safety follow-up period was 4.4 years in both ZOSTER-006 and ZOSTER-022.

Figure 13 Data collection for safety reporting In ZOSTER-006 and ZOSTER-022



[a] Unsolicited AEs with medically attended visit were recorded up to Month 8.
[b] Related to investigational vaccine, study participation or GSK concomitant medication/vaccine.
[c] Suspected cases of HZ and HZ-related complications were also collected during the entire study period.

Diary cards, provided to the subject at each vaccination visit, were used to collect **solicited symptoms** and **unsolicited AEs**. Subjects were trained on how to complete these diary cards. In all studies except ZOSTER-006 and ZOSTER-022, all subjects recorded solicited symptoms during the 7-day post-vaccination period and unsolicited AEs during the 30-day post-vaccination period either on separate diary cards or on the

same diary card but in separate sections. In ZOSTER-006 and ZOSTER-022, solicited local and general symptoms were recorded for 7 days after each vaccination on a 7-day diary card by subjects who were part of the 7-day diary card subset. The number of subjects in this subset was defined based on the empirical rules that, in absence of a specific AE in a cohort of N subjects, the probability is 95% that the incidence of that AE is less than 1/(N/3) [Hanley, 1983]. This subset included 9,946 subjects, of which 4,969 were in the HZ/su group and 4,977 were in the Placebo group.

All other AEs occurring during the 30-day post-vaccination period were recorded as unsolicited AEs on a 30-day diary card by the 7-day diary card subset of subjects. Subjects who did not belong to the 7-day diary card subset recorded all AEs occurring during the 30-day post-vaccination period as unsolicited AEs using a 30-day diary card. This implies that for these subjects, the unsolicited AEs recorded on the 30-day diary card also included the symptoms recorded as 'solicited' by the 7-day diary card subset.

Throughout the study, monthly phone calls or other contacts were put in place to collect events of interest, including SAEs, pIMDs, unsolicited AEs with medically attended visit, and HZ cases and HZ-related complications. Scripts were used to ensure collection was done in a standardized way between the different centers participating in the studies.

Unsolicited AEs, SAEs and pIMDs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a clinically validated international medical terminology dictionary developed and designed by the International Council for Harmonisation (ICH) for database entry, retrieval, evaluation, presentation of data and sharing of regulatory information for human medical products, standardly used across the pharmaceutical industry. For the analyses of safety data collected in all HZ/su studies, data were categorized according to MedDRA Preferred Terms (PTs) and System Organ Classes (SOCs). A PT is a distinct descriptor (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical social or family history characteristic. Related PTs are grouped into SOCs, which are groupings by etiology (e.g. Infections and infestations), manifestation site (e.g. Gastrointestinal disorders) or purpose (e.g. Surgical and medical procedures). Standardised MedDRA Queries (SMQs) are validated, pre-determined sets of MedDRA terms grouped together developed to facilitate retrieval of MedDRA-coded data in investigating drug safety issues and used to support safety analysis and reporting. Standardized and customized MedDRA queries were used to detect events of interest.

SAEs were collected during the 365-day post-vaccination period (up to Month 14). Although this was the primary pre-specified time period for follow-up of SAEs, all SAEs were reported during the entire study period. In addition, SAEs considered by the investigator to be vaccine-related and fatal SAEs were recorded during the entire study period.

pIMDs were collected during the entire study period. This assessment was done since there is a hypothetical concern regarding exacerbation or triggering of pIMDs associated with the immune-enhancing effects of the adjuvant (HZ/su contains the $AS01_B$) [Tavares, 2013]. The current methodology for the collection of pIMDs includes:

- A pre-defined list of pIMDs which contains specific disorders that likely represent an autoimmune or immune-mediated inflammatory process of interest. The list was provided in HZ/su study protocols and is used across all clinical development programs with vaccines using a combination of adjuvants or Adjuvant Systems, with the aim to focus investigator's attention to those events of interest (regardless of seriousness, new onset or exacerbation). This list was developed with and validated by an external panel of experts in autoimmune and inflammatory diseases and agreed with major authorities such as FDA. The list was updated in 2011 and 2014 to add other events. The most recent list updated on 30 June 2017 with the addition of gout as an AE of interest, is provided in Appendix Table 2.
- The pIMDs were collected up to at least 1 year post last vaccination (during the entire study period for ZOSTER-006 and ZOSTER-022) to detect late onset of events following vaccination, which is also in line with Regulatory Authority requirements for adjuvanted vaccines.
- The pre-defined list of pIMDs is linked to a customized MedDRA query for pIMDs which facilitates the identification of clinical trial, post-marketing surveillance and spontaneous reports in the clinical or safety databases during periodic searches for signal detection and evaluation.
- Disease-specific questionnaires (covering different PTs) are provided as general guidance for the relevant information that the investigator should pursue and provide to GSK in the Expedited Adverse Events Report (paper/electronic), if available. The aim is to have a sufficiently detailed clinical description allowing for a complete medical assessment of the case, determination of diagnostic certainty and possible causality i.e., relevant medical conditions (current and past), family history and relevant risk factors, clinical description of the event, relevant diagnostic test/exam results supporting the diagnosis, information on other possible causes of the event (e.g. concomitant medications and others illnesses), etc.

Unsolicited AEs with medically attended visit were evaluated in all subjects from Day 0 until Month 8.

Suspected cases of HZ and HZ-related complications were collected during the entire study period up to the DLP of 21 April 2015.

7.2.3. Assessment of Severity of Solicited Symptoms and Unsolicited AEs

In ZOSTER-006 and ZOSTER-022, as also for most other studies, all solicited symptoms and unsolicited AEs (including SAEs and pIMDs) were rated for severity by the investigator, who assigned the severity to one of the following categories: grade 1 (mild, AE easily tolerated by the subject, causing minimal discomfort and not interfering with normal activities), grade 2 (moderate, AE sufficiently discomforting to interfere with

normal activities), or grade 3 (severe, AE which prevented normal activities). The investigator assessed the maximum severity that occurred over the duration of the event for unsolicited AEs (including SAEs and pIMDs) reported during the study.

Grade 3 pain was defined as significant pain at rest which prevented normal activities. Grade 3 redness and swelling were defined as redness/swelling with a diameter >100 mm based on the US FDA guidelines for Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers enrolled in Preventive Vaccine Clinical Trials [FDA, 2007]. Grade 3 general symptoms (except for fever) were defined as symptoms preventing normal activity. Grade 3 fever (measured by oral, axillary or tympanic route) was defined as temperature >39.0°C/102.2°F.

7.2.4. Statistical Methods

7.2.4.1. Data sets analyzed and cohort definitions

In the main safety pooling, the analysis of reactogenicity (i.e., the solicited local and general symptoms) was performed on the TVC with 7-day diary card. The analysis of safety (unsolicited AEs, SAEs and pIMDs) was based on the TVC.

Since for subjects who were not part of the 7-day diary card subset, the unsolicited AEs recorded on the 30-day diary card also included the symptoms recorded as 'solicited' by the 7-day diary card subset, the results of the analysis of unsolicited AEs during the first 7 days post vaccination in the TVC were largely driven by the recording of symptoms which otherwise would have been included in the solicited symptom analysis. Therefore, as a secondary, supportive analysis, unsolicited AEs during the 30-day post-vaccination period were also analyzed on the TVC with 7-day diary card. In addition, unsolicited AEs were also analysed in the TVC from Day 0 to Day 6 post vaccination, and from Day 7 through Day 29 post vaccination.

In all individual studies, the primary analysis of safety was based on the TVC, which included all subjects with at least 1 vaccine administration documented. In ZOSTER-004, ZOSTER-006, ZOSTER-007, ZOSTER-022 and ZOSTER-033, the analysis in the ATP cohort for safety complemented the TVC analysis.

7.2.4.2. Statistical analysis of safety endpoints

Frequencies for the following safety endpoints were analyzed in the main safety pooling analysis:

- Solicited local/general symptoms during each 7-day (Days 0-6) post-vaccination period, including grade 3 solicited symptoms and solicited general symptoms with relationship to vaccination as assessed by the investigator (in the 7-day diary card subset of ZOSTER-006 and ZOSTER-022 only).
- Unsolicited AEs during the 30-day (Days 0-29) post-vaccination period, including grade 3 unsolicited AEs and unsolicited AEs considered related to vaccination by the investigator
- Unsolicited AEs with a medically attended visit up to Month 8.

- SAEs during the 30-day post-vaccination period, and 365 days post last vaccination period.
- Fatal SAEs and SAEs with causal relationship to vaccination during the 30-day post-vaccination period, 365 days post last vaccination period, and during the entire post-vaccination follow-up period.
- pIMDs during the 30-day post-vaccination period and during the 1-year post last vaccination period; and all pIMDs and pIMDs with causal relationship to vaccination during the entire post-vaccination follow-up period.

For the descriptive analyses, the percentage of subjects reporting a specific safety endpoint was tabulated with exact 95% CI. The descriptive analyses of all reactogenicity and safety endpoints were performed overall and stratified according to the 50-69 YOA and ≥70 YOA strata.

The comparative analysis in the main safety pooling was performed in order to assess the RR and estimate frequencies of safety events. An exploratory group comparison investigated the RR of developing individual unsolicited AEs or SAEs in subjects that received HZ/su as compared to subjects receiving Placebo. The nominal (unadjusted) p-value of 5% was used as a threshold to identify imbalances between the groups that may be related to vaccination; these events were further investigated. Of note, the use of such data mining analyses has the potential to identify a large number of events which may or may not have a causal relationship to vaccination due to multiplicity of endpoints. Therefore, a permutation test was performed to quantify the probability of erroneously identifying an event according to the p-value threshold.

In addition to this statistical approach, clinical judgment, including an evaluation of biological plausibility and temporal patterns, was also used to assess causality.

7.3. Extent of Exposure to AS01 in Vaccines

Clinical experience with AS01 in vaccines covers a wide range of populations with a variety of antigens, with >35,000 subjects having received at least one dose of vaccine containing AS01 in completed GSK-sponsored clinical trials, as of 30 June 2017 (Table 17).

The population of subjects vaccinated with an AS01-adjuvanted vaccine consists of >12,000 infants participating in trials with GSK's malaria vaccine *Mosquirix* (which has been assessed by the European Medicines Agency), >24,000 adults in trials with HZ/su, and subjects receiving other vaccine candidates in development for the adult/older adult population. These include vaccines against Hepatitis B, HIV, cytomegalovirus, Streptococcus, Non-Typeable Haemophilus influenzae and tuberculosis, as well as cancer immunotherapeutics. Note that the figure for HZ/su recipients represents combined exposure data presented in the BLA with data from other ZOSTER studies which have been completed as of 30 June 2017 and were not yet included in the BLA. Of note, GSK's malaria vaccine *Mosquirix* contains AS01 at half of the dose (i.e., 25 µg each of MPL and QS-21) used in HZ/su, a formulation known as $AS01_E$.

All AS01-containing vaccines have been shown to have clinically acceptable safety profiles. The reported AEs are primarily common injection-site symptoms (e.g., pain, redness and swelling) and general symptoms (e.g., myalgia, fatigue, and headache in adults, and fever in children). Consistently, when an AS01-adjuvanted vaccine formulation was compared to a non-adjuvanted vaccine or to a formulation containing another adjuvant or adjuvant combination (e.g., Aluminum salts, AS04, AS03), a higher rate of solicited symptoms was observed. However, these symptoms are typically mild to moderate in severity and self-limited.

Table 17 Clinical experience with AS01 in vaccines in GSK-sponsored completed studies as of 30 June 2017

Disease/Pathogen	Antigen (Adjuvant)	Age Groups studied	Exposure (subjects, n)
Herpes Zoster (shingles)/Varicella Zoster Virus	VZV gE ($AS01_{B/E}$)	Mainly older adults and elderly Other: young adults	20,513
Malaria/Plasmodium falciparum	RTS,S ($AS01_{B/E}$)	Mainly infants Other: children and young adults	12,971
Tuberculosis/Mycobacterium tuberculosis	M72 ($AS01_{B/E}$)	Mainly young adults and older adults Other: infants/children	707
Hepatitis B/Hepatitis B virus	HBsAg ($AS01_{B/E}$)	Young adults	402
AIDS/Human immunodeficiency virus	F4c0 gp120/NefTat ($AS01_{B/E}$)	Young adults	356
Anogenital cancer/Human papillomavirus	HPV-16/18/33/58 ($AS01_{B/E}$)	Young adults	268
Influenza Infection / Influenza virus	FLU ($AS01_{B/E}$)	Young adults, older adults and elderly	150
Pneumococcal infectious disease/ *Streptococcus pneumoniae*	11PCV ($AS01_{B/E}$)	Older adults/elderly	133
Non-typeable Haemophilus influenzae (NTHi) infection / NTHi	NTHi ($AS01_{E}$)	Older adults	60
Cytomegalovirus (CMV) infection/CMV	CMV gB ($AS01_{B}$)	Young adults and older adults	40
Antigen Specific Immunotherapeutic	MAGE-A3 ($AS01_{B}$) WT1 ($AS01_{B}$)	Mainly older adults and elderly Other: young adults	56
Total			**35,656**

$AS01_B$ is an Adjuvant System containing MPL, QS-21 and liposome (50 g MPL and 50 µg QS-21).
$AS01_E$ is an Adjuvant System containing MPL, QS-21 and liposome (25 g MPL and 25 µg QS-21).
Infants = Subjects aged 0-2 years (inclusive) at the time of first adjuvant vaccination
Children = Subjects aged 3-17 years (inclusive) at the time of first adjuvant vaccination
Young adults = Subjects aged 18-49 years (inclusive) at the time of first adjuvant vaccination
Older adults = Subjects aged 50-69 years (inclusive) at the time of first adjuvant vaccination
Elderly = Subjects aged ≥70 years at the time of first adjuvant vaccination
N = number of subjects vaccinated with AS01 adjuvanted vaccine
n = number of subjects in a given category

7.4. Analysis of Adverse Events in the Main Safety Pooling in All Subjects

7.4.1. Solicited Local and General Symptoms

Solicited local and general symptoms were analyzed in the TVC with 7-day diary card from the main safety pooling. As expected with potent adjuvanted vaccines, solicited local and general symptoms were more frequently reported after administration of HZ/su compared to Placebo, regardless of age. At least one solicited local symptom during the 7-day post-vaccination period was experienced by 80.8% of subjects in the HZ/su group and 11.7% of subjects in the Placebo group, and at least one solicited general symptom was experienced by 64.8% and 29.1% of subjects, respectively. The most common solicited local symptom was pain, reported by 78.0% and 10.9% of subjects, respectively. The most frequently reported solicited general symptoms were myalgia (44.7% and 11.7%, respectively), fatigue (44.5% and 16.5%, respectively) and headache (37.7% and 15.5%, respectively).

The incidence of solicited local (Table 18) and general (Table 19) symptoms was lower in adults ≥70 YOA compared to adults 50-69 YOA. All solicited local symptoms were by default considered related to vaccination, while most of the solicited general symptoms were also considered related to vaccination by the investigator.

Grade 3 solicited local (Table 18) and general (Table 19) symptoms were reported by respectively ≤8.6% and ≤7.1% of subjects vaccinated with HZ/su. The most frequently reported grade 3 symptoms were grade 3 pain, myalgia and fatigue.

In the HZ/su group, the incidence of solicited local symptoms was similar after Dose 1 and Dose 2, whereas there was an increase in the incidence of solicited general symptoms (symptoms of any grade and grade 3 symptoms) from Dose 1 to Dose 2 (Table 20).

The majority of solicited local and general symptoms reported with HZ/su were mild to moderate in severity, and self-limited with a median duration of ≤3 days for solicited local symptoms and ≤2 days for solicited general symptoms.

The compliance to the two-dose schedule was high in both groups in the main safety pooling, i.e., 95.0% of subjects in the HZ/su group and 96.0% of subjects in the Placebo group received 2 vaccine doses.

Table 18 Main safety pooling analysis: Incidence of solicited local symptoms reported during the 7-day post-vaccination period in adults 50-69 YOA and ≥70 YOA overall per subject (TVC with 7-day diary card)

		50-69 YOA								≥70 YOA							
		HZ/su N=2626				Placebo N=2617				HZ/su N=2258				Placebo N=2263			
Symptom	**Type**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Pain	All	2248	**85.6**	84.2	86.9	334	**12.8**	11.5	14.1	1562	**69.2**	67.2	71.1	199	**8.8**	7.7	10.0
	Grade 3	225	8.6	7.5	9.7	13	0.5	0.3	0.8	90	4.0	3.2	4.9	4	0.2	0.0	0.5
Redness (mm)	All	1012	**38.5**	36.7	40.4	37	**1.4**	1.0	1.9	851	**37.7**	35.7	39.7	27	**1.2**	0.8	1.7
	>100	71	2.7	2.1	3.4	0	0.0	0.0	0.1	70	3.1	2.4	3.9	0	0.0	0.0	0.2
Swelling (mm)	All	748	**28.5**	26.8	30.3	23	**0.9**	0.6	1.3	519	**23.0**	21.3	24.8	25	**1.1**	0.7	1.6
	>100	21	0.8	0.5	1.2	0	0.0	0.0	0.1	30	1.3	0.9	1.9	0	0.0	0.0	0.2

N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum

Table 19 Main safety pooling analysis: Incidence of solicited general symptoms reported during the 7-day post-vaccination period in adults 50-69 YOA and ≥70 YOA overall per subject (TVC with 7-day diary card)

		50-69 YOA								≥70 YOA							
		HZ/su N=2624				Placebo N=2617				HZ/su N=2252				Placebo N=2264			
Symptom	**Type**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
Fatigue	All	1347	**51.3**	49.4	53.3	479	**18.3**	16.8	19.8	825	**36.6**	34.6	38.7	326	**14.4**	13.0	15.9
	Grade 3	178	6.8	5.9	7.8	33	1.3	0.9	1.8	79	3.5	2.8	4.4	17	0.8	0.4	1.2
Gastrointestinal symptoms	All	538	**20.5**	19.0	22.1	254	**9.7**	8.6	10.9	304	**13.5**	12.1	15.0	172	**7.6**	6.5	8.8
	Grade 3	40	1.5	1.1	2.1	17	0.6	0.4	1.0	26	1.2	0.8	1.7	10	0.4	0.2	0.8
Headache	All	1185	**45.2**	43.2	47.1	487	**18.6**	17.1	20.2	653	**29.0**	27.1	30.9	268	**11.8**	10.5	13.2
	Grade 3	128	4.9	4.1	5.8	24	0.9	0.6	1.4	34	1.5	1.0	2.1	10	0.4	0.2	0.8
Myalgia	All	1390	**53.0**	51.0	54.9	345	**13.2**	11.9	14.5	790	**35.1**	33.1	37.1	225	**9.9**	8.7	11.2
	Grade 3	186	7.1	6.1	8.1	23	0.9	0.6	1.3	62	2.8	2.1	3.5	10	0.4	0.2	0.8
Shivering	All	868	**33.1**	31.3	34.9	171	**6.5**	5.6	7.5	439	**19.5**	17.9	21.2	110	**4.9**	4.0	5.8
	Grade 3	149	5.7	4.8	6.6	7	0.3	0.1	0.6	49	2.2	1.6	2.9	6	0.3	0.1	0.6
Temperature (°C)	All	679	**25.9**	24.2	27.6	84	**3.2**	2.6	4.0	323	**14.3**	12.9	15.9	61	**2.7**	2.1	3.4
	>39.0	11	0.4	0.2	0.7	5	0.2	0.1	0.4	3	0.1	0.0	0.4	3	0.1	0.0	0.4

N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once when the intensity is maximum

Table 20 Main safety pooling analysis: Incidence of solicited local and general symptoms reported during the 7-day post-vaccination period following each dose in the HZ/su group (TVC with 7-day diary card)

		Dose 1					Dose 2				
					95 % CI					95 % CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Local Symptoms											
Pain	All	4861	3417	**70.3**	69.0	71.6	4699	3089	**65.7**	64.4	67.1
	Grade 3	4861	171	3.5	3.0	4.1	4699	197	4.2	3.6	4.8
Redness (mm)	All	4861	1368	**28.1**	26.9	29.4	4699	1288	**27.4**	26.1	28.7
	>100	4861	91	1.9	1.5	2.3	4699	71	1.5	1.2	1.9
Swelling (mm)	All	4861	895	**18.4**	17.3	19.5	4699	830	**17.7**	16.6	18.8
	>100	4861	30	0.6	0.4	0.9	4699	25	0.5	0.3	0.8
General Symptoms											
Fatigue	All	4847	1499	**30.9**	29.6	32.2	4697	1578	**33.6**	32.2	35.0
	Grade 3	4847	117	2.4	2.0	2.9	4697	166	3.5	3.0	4.1
GI symptoms†	All	4847	490	**10.1**	9.3	11.0	4697	532	**11.3**	10.4	12.3
	Grade 3	4847	33	0.7	0.5	1.0	4697	36	0.8	0.5	1.1
Headache	All	4847	1184	**24.4**	23.2	25.7	4697	1325	**28.2**	26.9	29.5
	Grade 3	4847	69	1.4	1.1	1.8	4697	109	2.3	1.9	2.8
Myalgia	All	4847	1552	**32.0**	30.7	33.4	4697	1587	**33.8**	32.4	35.2
	Grade 3	4847	110	2.3	1.9	2.7	4697	167	3.6	3.0	4.1
Shivering	All	4847	670	**13.8**	12.9	14.8	4697	1006	**21.4**	20.3	22.6
	Grade 3	4847	70	1.4	1.1	1.8	4697	144	3.1	2.6	3.6
Fever* (°C)	All	4847	539	**11.1**	10.2	12.0	4697	683	**14.5**	13.5	15.6
	>39.0	4847	7	0.1	0.1	0.3	4697	8	0.2	0.1	0.3

N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
* Fever defined as ≥37.5°C/99.5°F for oral, axillary or tympanic route, or ≥38°C/100.4°F for rectal route.
† GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain

7.4.2. Unsolicited Adverse Events

Table 21 presents the RR between groups of subjects reporting unsolicited AEs classified by SOC and PT within the 30-day post-vaccination period in the TVC of the main safety pooling. The table only lists AEs with an incidence ≥1.0% in the HZ/su group and with an unadjusted p-value <0.05, and events are sorted by SOC and by incidence in the HZ/su group. Unsolicited AEs were reported more frequently in the HZ/su group compared to the Placebo group, and this observation was statistically significant, i.e., by 7,393 subjects (50.5%) in the HZ/su group, and by 4,689 subjects (32.0%) in the Placebo group (RR = 1.6 [95% CI: 1.5, 1.6], unadjusted p-value <0.001). Note that this imbalance is mainly due to the fact that subjects who were not included in the 7-day diary card subset have reported expected local and general symptoms as unsolicited AEs. Indeed, the majority of these more frequently reported unsolicited AEs in the HZ/su group were the local and general symptoms recorded as solicited symptoms by subjects who were part of the 7-day diary card subset, i.e., a subset of 9,946 subjects who were randomly selected to report pre-specified local injection site symptoms (i.e., pain, redness and swelling) and general symptoms (i.e., fever, headache, fatigue, chills [shivering], myalgia

and nausea) on a 7-day diary card designed for this purpose (indicated in *italics* in Table 21).

In addition to the 'solicited' symptoms mentioned above, 4 unsolicited AEs were reported with an incidence ≥1.0% in HZ/su recipients, and at least twice as often in the HZ/su group compared to the Placebo group. These events included injection site pruritus (2.16% in the HZ/su group and 0.24% in the Placebo group; RR = 9.07), malaise (1.73% and 0.29%, respectively; RR = 5.91), pain (1.39% and 0.23%, respectively; RR = 6.01), and injection site warmth (1.02% and 0.03%, respectively; RR = 29.83) (indicated in **bold** in Table 21). Pain and injection site warmth were already captured as part of the solicited symptoms listed above, therefore only malaise and pruritus are added to the list of other adverse reactions reported in the proposed PI.

Furthermore, following an assessment of risks of inflammation after exposure to HZ/su, a numerical imbalance in the reporting rate of gout (including gouty arthritis) as unsolicited AE was identified for which a biologically plausible relationship with vaccination cannot be excluded at this point. Further details are provided in Section 7.4.5.2.

Table 21 Main safety pooling analysis: RR of unsolicited AEs classified by SOC and PT within the 30-day post-vaccination period (incidence ≥1.0% in the HZ/su group and unadjusted p-value <0.05) (TVC)

		HZ/su N = 14645				Placebo N = 14660				Relative Risk (HZ/su over Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**RR**	**LL**	**UL**	**P-Value**
Any symptom		7393	50.48	49.67	51.29	4689	31.98	31.23	32.75	1.58	1.52	1.64	<0.001
General disorders and administration site conditions (10018065)	*Injection site pain (10022086)*	*3365*	*22.98*	*22.30*	*23.67*	*252*	*1.72*	*1.51*	*1.94*	*13.37*	*11.76*	*15.25*	*<0.001*
	Injection site erythema (10022061)	*1357*	*9.27*	*8.80*	*9.75*	*37*	*0.25*	*0.18*	*0.35*	*36.71*	*26.50*	*52.37*	*<0.001*
	Pyrexia (10037660)	*1037*	*7.08*	*6.67*	*7.51*	*76*	*0.52*	*0.41*	*0.65*	*13.66*	*10.81*	*17.48*	*<0.001*
	Injection site swelling (10053425)	*1014*	*6.92*	*6.52*	*7.35*	*22*	*0.15*	*0.09*	*0.23*	*46.14*	*30.30*	*73.96*	*<0.001*
	Fatigue (10016256)	*522*	*3.56*	*3.27*	*3.88*	*140*	*0.95*	*0.80*	*1.13*	*3.73*	*3.09*	*4.53*	*<0.001*
	Chills (10008531)	*516*	*3.52*	*3.23*	*3.83*	*35*	*0.24*	*0.17*	*0.33*	*14.76*	*10.47*	*21.42*	*<0.001*
	Injection site pruritus (10022093)	**317**	**2.16**	**1.94**	**2.41**	**35**	**0.24**	**0.17**	**0.33**	**9.07**	**6.38**	**13.25**	**<0.001**
	Malaise (10025482)	**254**	**1.73**	**1.53**	**1.96**	**43**	**0.29**	**0.21**	**0.39**	**5.91**	**4.27**	**8.37**	**<0.001**
	Pain (10033371)	**204**	**1.39**	**1.21**	**1.60**	**34**	**0.23**	**0.16**	**0.32**	**6.01**	**4.16**	**8.91**	**<0.001**
	Injection site warmth (10022112)	**149**	**1.02**	**0.86**	**1.19**	**5**	**0.03**	**0.01**	**0.08**	**29.83**	**12.50**	**93.22**	**<0.001**
Nervous system disorders (10029205)	*Headache (10019211)*	*954*	*6.51*	*6.12*	*6.93*	*445*	*3.04*	*2.76*	*3.33*	*2.15*	*1.92*	*2.41*	*<0.001*
	Dizziness (10013573)	182	1.24	1.07	1.44	113	0.77	0.64	0.93	1.61	1.27	2.06	<0.001
Infections and infestations (10021881)	Upper respiratory tract infection (10046306)	231	1.58	1.38	1.79	182	1.24	1.07	1.43	1.27	1.04	1.55	<0.05

		HZ/su N = 14645				Placebo N = 14660				Relative Risk (HZ/su over Placebo)			
				95% CI				95% CI			95% CI*		
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL	RR	LL	UL	P-Value
Musculoskeletal and connective tissue disorders (10028395)	*Myalgia (10028411)*	*478*	*3.26*	*2.98*	*3.56*	*105*	*0.72*	*0.59*	*0.87*	*4.56*	*3.68*	*5.68*	*<0.001*
	Arthralgia (10003239)	252	1.72	1.52	1.94	171	1.17	1.00	1.35	1.48	1.21	1.80	<0.001
	Pain in extremity (10033425)	155	1.06	0.90	1.24	107	0.73	0.60	0.88	1.45	1.13	1.87	<0.01
Gastrointestinal disorders (10017947)	*Nausea (10028813)*	*197*	*1.35*	*1.16*	*1.55*	*69*	*0.47*	*0.37*	*0.60*	*2.86*	*2.16*	*3.82*	*<0.001*

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI* = 95% confidence interval for relative risk (Exact Conditional to total number of cases)
P-Value = 2-sided Exact Test conditional to number of cases

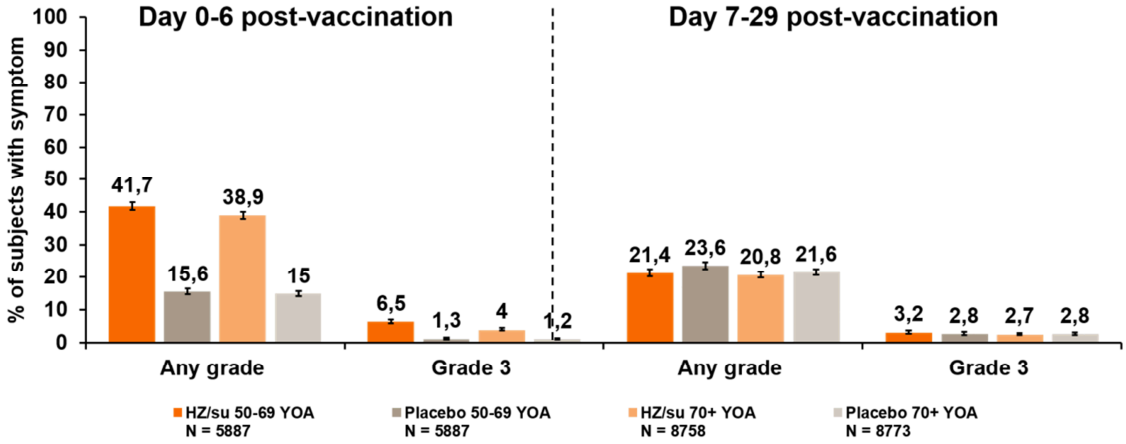
To provide further details on the higher incidence of unsolicited AEs in the HZ/su group in the TVC during the 30-day post-vaccination period, the incidence of unsolicited AEs was analyzed in the overall TVC during the Days 0-6 and Days 7-29 post-vaccination periods (Figure 14). Within the 7-day post-vaccination period, the incidence of unsolicited AEs was higher in the HZ/su group (40.0%) compared to the Placebo group (15.2%), while the incidence during the Days 7-29 post-vaccination period was similar for both groups (21.0% and 22.4%, respectively), reflecting the fact that the differences in reporting rates of unsolicited AEs between the HZ/su and Placebo groups are due to the expected short-term local and general reactions covered by the solicited symptoms list. In addition, in the TVC with 7-day diary card, the incidence of unsolicited AEs during the 30-day post-vaccination period was similar between the HZ/su group (29.2%) and the Placebo group (27.5%).

In the TVC within the 30-day post-vaccination period, grade 3 unsolicited AEs were reported by 7.5% and 3.8% of subjects who received HZ/su and Placebo, respectively.

By age stratum in the TVC, unsolicited AEs were reported by 51.4% of HZ/su recipients and 33.2% of Placebo recipients in the 50-69 YOA stratum, and by respectively 49.9% and 31.1% of subjects in the ≥70 YOA stratum.

In conclusion, when the expected symptoms occurring during the initial 7-day follow-up period are considered separately, the overall incidence of unsolicited AEs was comparable between the HZ/su and Placebo groups. The differences in incidence observed in the TVC during the 7-day post vaccination period were driven by the local and general reactions occurring soon after vaccination and collected as solicited symptoms by subjects in the 7-day diary card subset, which is similar to what was observed in the early development program.

Figure 14 Main safety pooling analysis: Percentage of subjects reporting the occurrence of unsolicited AEs and grade 3 unsolicited AEs within Days 0-6 and Days 7-29 post-vaccination periods (TVC)



N = number of subjects with at least one documented dose
% = percentage of subjects reporting the symptom at least once

7.4.3. Serious Adverse Events

An overview of the incidence of any SAEs and SAEs considered related to vaccination by the investigator by time period, overall and by age stratum in the TVC, is presented in Table 22.

The rates of SAEs were similar between the HZ/su and Placebo groups for all time periods analyzed. From the first administered dose up to 30 days post last vaccination, SAEs were reported by 342 subjects (2.3%) in the HZ/su group and 327 subjects (2.2%) in the Placebo group. From the first administered dose up to 365 days post last vaccination, SAEs were reported by 1,482 subjects (10.1%) and 1,525 subjects (10.4%), respectively. During the entire post-vaccination follow-up period, SAEs were reported by 1,880 subjects (12.8%) and 1,945 subjects (13.3%), respectively. By age stratum, SAEs were reported with a higher incidence by adults ≥70 YOA compared to adults 50-69 YOA.

Most SAEs considered related to vaccination by the investigator were reported from the first administered dose up to 365 days post last vaccination, i.e., by 15 subjects (0.1%) receiving HZ/su and by 13 subjects (0.1%) receiving Placebo.

Table 22 Main safety pooling analysis: Percentage of subjects reporting the occurrence of at least one SAE by time period, overall and by age stratum (TVC)

	50-69 YOA								≥70 YOA								Overall							
	HZ/su N= 5887				Placebo N= 5887				HZ/su N= 8758				Placebo N= 8773				HZ/su N=14645				Placebo N=14660			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
Time period	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
All SAEs																								
≤30 days post last vaccination	81	**1.4**	1.1	1.7	79	**1.3**	1.1	1.7	261	**3.0**	2.6	3.4	248	**2.8**	2.5	3.2	342	**2.3**	2.1	2.6	327	**2.2**	2.0	2.5
≤365 days post last vaccination	367	**6.2**	5.6	6.9	359	**6.1**	5.5	6.7	1115	**12.7**	12.0	13.4	1166	**13.3**	12.6	14.0	1482	**10.1**	9.6	10.6	1525	**10.4**	9.9	10.9
Entire post-vaccination follow-up period	433	**7.4**	6.7	8.1	424	**7.2**	6.6	7.9	1447	**16.5**	15.7	17.3	1521	**17.3**	16.6	18.1	1880	**12.8**	12.3	13.4	1945	**13.3**	12.7	13.8
SAEs considered related to vaccination by the investigator																								
≤30 days post last vaccination	1	**0.0**	0.0	0.1	3	**0.1**	0.0	0.1	7	**0.1**	0.0	0.2	5	**0.1**	0.0	0.1	8	**0.1**	0.0	0.1	8	**0.1**	0.0	0.1
≤365 days post last vaccination	3	**0.1**	0.0	0.1	6	**0.1**	0.0	0.2	12	**0.1**	0.1	0.2	7	**0.1**	0.0	0.2	15	**0.1**	0.1	0.2	13	**0.1**	0.0	0.2
Entire post-vaccination follow-up period	3	**0.1**	0.0	0.1	7	**0.1**	0.0	0.2	12	**0.1**	0.1	0.2	8	**0.1**	0.0	0.2	15	**0.1**	0.1	0.2	15	**0.1**	0.1	0.2

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

No statistically significant imbalances between the HZ/su and Placebo group have been observed in terms of the overall incidence of SAEs (including fatal SAEs) reported from the first administered dose up to 365 days post last vaccination, i.e., respectively 10.1% (95% CI: 9.6, 10.6) and 10.4% (95% CI: 9.9, 10.9) (RR = 0.9 [95% CI: 0.9, 1.1], unadjusted p-value = 0.46).

Results of the comparative analysis for the most frequently reported SAEs in the HZ/su group from the first administered dose up to 365 days post last vaccination are presented in Figure 15 by SOC and in Figure 16 by PT as forest plots. These plots show the point estimate of the RR including the 95% CI.

For SOCs reported with an incidence ≥0.5% in the HZ/su group (Figure 15), the 95% CIs for the RR included the value of 1 for all but 1 SOC, and the p-values were all non-significant (unadjusted p-value <0.05). Only vascular disorders were reported significantly more frequently in the Placebo group (129 subjects; 0.9%) compared to the HZ/su group (96 subjects; 0.7%) (RR = 0.7 [95% CI: 0.6, 1.0], unadjusted p-value = 0.03). For all other SOCs reported with an incidence <0.5% in the HZ/su group, there were no statistically significant imbalances between the groups.

For PTs reported with an incidence ≥0.2% in the HZ/su group (Figure 16), the 10 most frequently reported SAEs up to 365 days post last vaccination included pneumonia, cardiac events and atherosclerotic events, as expected in this population of adults ≥50 YOA. A few categories of SAEs (by PT) with an incidence <0.2% in the HZ/su group were reported significantly more frequently, either in the HZ/su or in the Placebo group (unadjusted p-value <0.05):

- One individual SAE (by PT) was reported significantly more frequently in the HZ/su group compared to the Placebo group: supraventricular tachycardia, reported by 6 subjects (<0.05%) in the HZ/su group and not reported in the Placebo group (RR = INF [95% CI: 1.6, INF], unadjusted p-value = 0.03). In view of this observation, other PTs referring to the same medical context were evaluated (i.e. arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, cardiac flutter, supraventricular tachycardia, tachyarrhythmia and tachycardia paroxysmal). The data showed no imbalance between the groups when grouping all these PTs (0.5% [95% CI: 0.4, 0.6] in both the HZ/su and Placebo groups; RR=1.1 [95% CI: 0.7, 1.5], unadjusted p-value = 0.86).
- Three SAEs were reported significantly more frequently in the Placebo group compared to the HZ/su group:
  - aortic stenosis (no subjects in the HZ/su group and 10 subjects [0.07%] in the Placebo group; RR = 0.00 [95% CI: 0.00, 0.35], unadjusted p-value = 0.0020)
  - cardio-respiratory arrest (0 and 6 [0.04%] subjects, respectively; RR = 0.00 [95% CI: 0.00, 0.65], unadjusted p-value = 0.0313)
  - retinal detachment (1 [0.01%] and 8 [0.05%] subjects, respectively; RR = 0.13 [95% CI: 0.00, 0.93], unadjusted p-value = 0.0392).

Additional analyses were performed to evaluate major adverse cardiovascular and cerebrovascular events, of which the results are provided below in Section 7.4.3.1. Overall, there were no relevant imbalances observed in any of the groups. Based on the review of available safety data on SAEs, no safety concerns have been identified.

Figure 15 Main safety pooling analysis: Relative Risk between groups of subjects reporting the occurrence of SAEs for the most frequently reported MedDRA SOCs (≥0.5% in HZ/su group), from first vaccination up to 365 days post last vaccination (TVC)

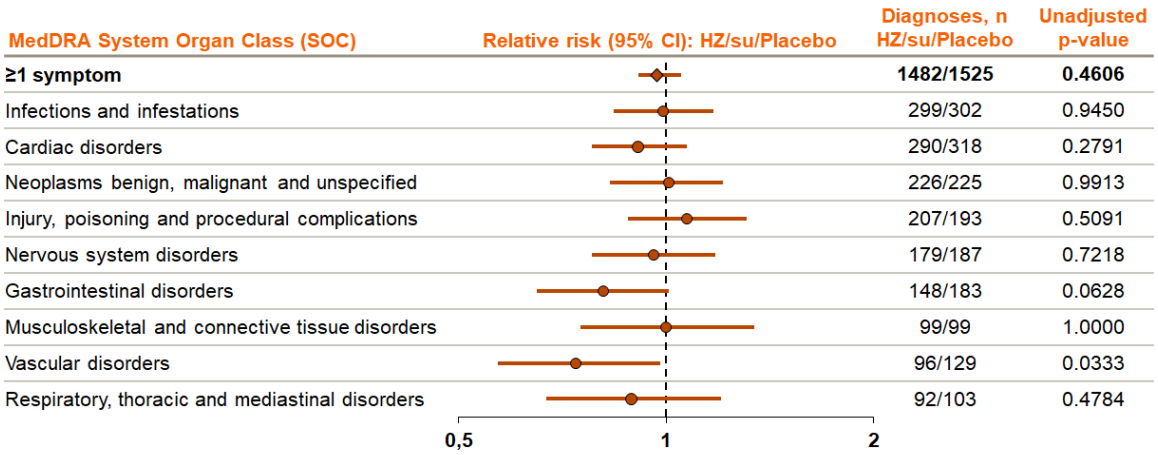
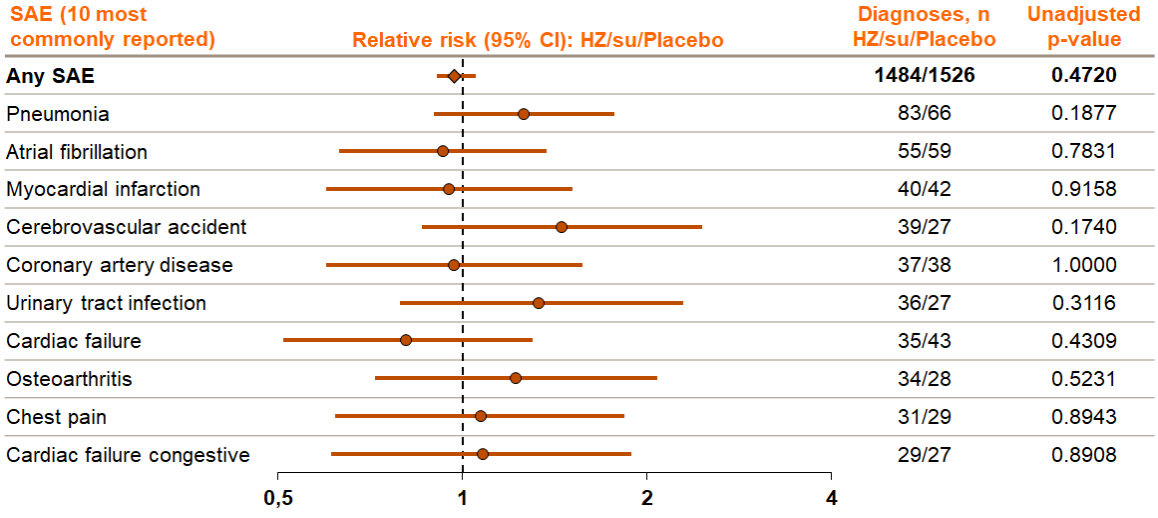


Figure 16 Main safety pooling analysis: Relative Risk between groups of subjects reporting the occurrence of the 10 most frequently reported SAEs (≥0.2% in HZ/su group) by MedDRA PT from first vaccination up to 365 days post last vaccination (TVC)



7.4.3.1. Major adverse cardiac and cerebrovascular events

In the target study population, cardiovascular and cerebrovascular diseases are the major causes of morbidity and mortality and therefore, these events have been considered of special interest in the target population of adults ≥50 YOA.

Cardiovascular heart disease represents the leading cause of death worldwide in both men and women ≥65 YOA. In the US in 2014, CDC data reported a prevalence of death in the American population aged ≥55 YOA of 0.17% for death related to coronary heart disease, 0.09% for lung disease, 0.08% for lung cancer, and 0.08% for stroke [USA LifeExpectancy, 2017]. The prevalence of sudden cardiac death varies by gender and age. However, an observed proportion of 0.2% was shown in people ≥55 YOA [Chugh, 2004], and the incidence of in-hospital cardiac arrest in patients ≥65 YOA is 2.2 per 1,000 person-years [Churpek, 2015, Sandroni, 2016].

In Europe, for people ≥65 YOA, the following standardized death rates were recorded in 2013: 594 deaths per 100,000for ischemic heart diseases, followed by 418 per 100,000 for cerebrovascular diseases, 385 per 100,000 for respiratory diseases and 200 per 100,000 for lung cancer. Between 2011 and 2014, the average death rates for myocardial infarction and pneumonia were respectively 216 and 120 per 100,000 [Eurostat, 2016].

Major adverse cardiovascular and cerebrovascular events, including fatal or non-fatal cardiac arrest, acute myocardial infarction and other ischemic heart disease, congestive heart failure, new cardiac arrhythmia, and fatal or non-fatal stroke (embolic, thrombotic, or hemorrhagic events) were selected for further analyses. In order to retrieve any potential cases featuring major adverse cardiovascular and cerebrovascular events, a search was performed using the following SMQs (MedDRA v.18.0 SMQs, "narrow" search) and individual PTs:

- Cerebrovascular events: haemorrhagic cerebrovascular conditions (SMQ), ischaemic cerebrovascular conditions (SMQ).
- Cardiac events: ischaemic heart disease (SMQ), cardiac failure (SMQ), cardiac arrhythmias (SMQ), cardiac arrest (customized MedDRA Query, with following PTs: cardiac arrest, cardio-respiratory arrest, sudden cardiac death, cardiac death, and sinus arrest).

The outcomes of interest were analyzed in the TVC of the main safety pooling for subjects reporting the occurrence of unsolicited AEs within the 30-day post-vaccination period and SAEs from first vaccination up to 365 days post last vaccination. The RR was estimated by comparing the results of the above searches between the HZ/su and Placebo groups. Results of the comparative analysis for both periods analyzed are presented in Table 23. None of the categories of cardiac and cerebrovascular events (SMQ) were reported statistically significantly more frequently in either of the groups (unadjusted p-value <0.05). Overall, there were no relevant imbalances observed in any of the groups. Based on the review of available safety data on major adverse cardiovascular and cerebrovascular events selected for further analyses, no safety concerns have been identified.

Table 23 Main safety pooling analysis: Relative Risk between groups of subjects reporting the occurrence of unsolicited and serious major adverse cardiovascular and cerebrovascular events classified by MedDRA SMQ (TVC)

SMQ	Unsolicited events within the 30-day post-vaccination period*											SAEs from the first vaccination up to 365 days post last vaccination*										
	HZ/su N=14645				Placebo N=14660				Relative Risk (HZ/su over Placebo)			HZ/su N=14645				Placebo N=14660				Relative Risk (HZ/su over Placebo)		
			95% CI				95% CI			95% CI**				95% CI				95% CI			95% CI**	
	n	%	LL	UL	n	%	LL	UL	RR	LL	UL	n	%	LL	UL	n	%	LL	UL	RR	LL	UL
Haemorrhagic cerebrovascular conditions	10	**0.07**	0.03	0.13	13	**0.09**	0.05	0.15	0.77	0.30	1.90	55	**0.38**	0.28	0.49	53	**0.36**	0.27	0.47	1.04	0.70	1.54
Ischaemic cerebrovascular conditions	19	**0.13**	0.08	0.20	23	**0.16**	0.10	0.24	0.83	0.43	1.59	99	**0.68**	0.55	0.82	86	**0.59**	0.47	0.72	1.15	0.85	1.56
Ischaemic heart disease	29	**0.20**	0.13	0.28	40	**0.27**	0.19	0.37	0.73	0.43	1.20	140	**0.96**	0.80	1.13	155	**1.06**	0.90	1.24	0.90	0.71	1.14
Cardiac failure	11	**0.08**	0.04	0.13	16	**0.11**	0.06	0.18	0.69	0.29	1.58	73	**0.50**	0.39	0.63	82	**0.56**	0.45	0.69	0.89	0.64	1.24
Cardiac arrhythmias	35	**0.24**	0.17	0.33	39	**0.27**	0.19	0.36	0.90	0.55	1.46	90	**0.61**	0.49	0.75	99	**0.68**	0.55	0.82	0.91	0.68	1.22
Cardiac arrest	0	**0.00**	0.00	0.03	2	**0.01**	0.00	0.05	0.00	0.00	3.48	5	**0.03**	0.01	0.08	14	**0.10**	0.05	0.16	0.36	0.10	1.05

* At least one symptom experienced per SMQ (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting any Preferred Term part of the SMQ at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit
95% CI** = 95% confidence interval for relative risk (Exact Conditional to total number of cases)
P-Value = unadjusted p-value; 2-sided Exact Test conditional to number of cases

7.4.4. Fatal Serious Adverse Events

An overview of the incidence of fatal SAEs by time period, overall and by age stratum in the TVC is presented in Table 24.

Fatal SAEs were reported at comparable rates by subjects in the HZ/su and Placebo groups for all time periods analyzed. From the first administered dose up to 30 days post last vaccination, 17 subjects (0.1%)in the HZ/su group and 21 subjects (0.1%) in the Placebo group reported fatal SAEs, while up to 365 days post last vaccination, fatal SAEs were reported by 153 subjects (1.0%) and 168 subjects (1.1%), respectively. The majority of fatal SAEs had a time to onset of longer than 1 year post last vaccination; during the entire post-vaccination follow-up period, fatal SAEs were reported by 634 subjects (4.3%) and 680 subjects (4.6%), respectively.

The most common fatal SAEs during the entire post-vaccination follow-up period were reported under the SOCs of neoplasms, cardiac disorders and infections and infestations. By PT, fatal SAEs reported by ≥0.2% of subjects in the HZ/su group were cardiac failure (0.3% in the HZ/su group and 0.4% in the Placebo group), pneumonia and myocardial infarction (0.3% and 0.3%, respectively), death (not otherwise specified; 0.2% and 0.3%, respectively), cardiac arrest (0.2% and 0.2%, respectively) and lung neoplasm malignant (0.2% and 0.1%, respectively). These most frequently reported events and categories of fatal SAEs are expected in this population of adults ≥50 YOA.

By age range in the 50-69 YOA and ≥70 YOA strata, the majority of fatal SAEs during the entire post-vaccination follow-up period were reported by adults ≥70 YOA (6.2% and 6.6% of subjects in the HZ/su and Placebo groups, respectively), while in adults 50-69 YOA, fatal SAEs were reported by 1.6% and 1.7% of subjects, respectively.

One fatal SAE of neutropenic sepsis was considered by the investigator as related to vaccination, and was reported in a Canadian subject in the HZ/su group of ZOSTER-022. This event concerned a 90-year old male subject of African heritage who was diagnosed with acute myeloid leukemia (AML) 75 days after receiving the first and only dose of HZ/su. He was hospitalized and was withdrawn from study treatment. The subject was treated with blood transfusion, chemotherapy (azacitidine and allopurinol) and ondansetron and was discharged from hospital. The patient consulted the ER 96 days after vaccination, for non-bloody diarrhea, cough and mild dyspnea. He was re-admitted to hospital with a diagnosis of febrile neutropenia. The subject's status decompensated quickly over the next 24 hours and he died (b) (6) days after vaccination), due to neutropenic sepsis. Medical history at baseline included a longstanding and stable autoimmune thrombocytopenic purpura, with a consistently low platelet count between ranges of 101-135 x 10^9/L since diagnosis (normal range: 150-400 x 10^9/L). Other medical conditions included chronic hypertension, cardiovascular disease (right atrium enlargement, mild left ventricular hypertrophy, heart valve incompetence, a coronary artery bypass) and diabetes mellitus. The investigator assessed as possible causes of the neutropenic sepsis in this subject: the AML, the pre-existing autoimmune thrombocytopenic purpura and the study vaccine HZ/su. GSK considers that the age of the subject, the long time to onset of the neutropenic sepsis after vaccination (over 3 months), the subject's underlying medical conditions as well as the nature of the event

(no biological plausibility), make a possible causal association between the neutropenic sepsis and the administration of HZ/su unlikely. The neutropenia and neutropenic sepsis were likely a result of the induction chemotherapy for AML. Neutropenic fever and septic infections are common in patients with AML. The treatment protocol of AML induces long lasting periods of neutropenia, which predisposes patients to recurring or fatal infections.

Table 24 Main safety pooling analysis: Percentage of subjects reporting the occurrence of at least one fatal SAE by time period, overall and by age stratum (TVC)

	50-69 YOA								≥70 YOA								Overall							
	HZ/su N= 5887				Placebo N= 5887				HZ/su N= 8758				Placebo N= 8773				HZ/su N=14645				Placebo N=14660			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
Time period	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
≤30 days post last vaccination	3	**0.1**	0.0	0.1	3	**0.1**	0.0	0.1	14	**0.2**	0.1	0.3	18	**0.2**	0.1	0.3	17	**0.1**	0.1	0.2	21	**0.1**	0.1	0.2
≤365 days post last vaccination	28	**0.5**	0.3	0.7	27	**0.5**	0.3	0.7	125	**1.4**	1.2	1.7	141	**1.6**	1.4	1.9	153	**1.0**	0.9	1.2	168	**1.1**	1.0	1.3
Entire post-vaccination follow-up period	95	**1.6**	1.3	2.0	100	**1.7**	1.4	2.1	539	**6.2**	5.7	6.7	580	**6.6**	6.1	7.2	634	**4.3**	4.0	4.7	680	**4.6**	4.3	5.0

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

7.4.5. Events of special interest

7.4.5.1. Potential Immune-Mediated Diseases (pIMDs)

The rationale for the monitoring of pIMDs for all vaccines containing Adjuvant Systems, including $AS01_B$, relates to their possible effects on the regulation of the immune system and the theoretical risk that they may induce unwanted immune processes in susceptible individuals. In immune-mediated inflammatory disorders, tissue damage results from self-directed inflammation due to activation of innate immune cells, including macrophages and neutrophils. By contrast, autoimmune diseases can be classified as inflammation against self that is mediated by the adaptive immune system, with development of immune reactivity towards native antigens.

HZ/su may bring benefit to patients with autoimmune diseases such as rheumatoid arthritis, psoriasis, systemic lupus erythematosus, inflammatory bowel diseases, Crohn's disease and multiple sclerosis, including patients on immunosuppressant chronic treatment, as there is a significant medical need in these patients due to the high incidence of HZ [Yun, 2016]. Although HZ in this subgroup of patients represents a small proportion of the total number of HZ cases, patients with immune function altering conditions contribute substantially to the public health burden because of their higher risk for HZ and HZ complications, including persistent post-HZ pain and PHN [Chen, 2014a]. Therefore, the availability of an HZ vaccine for subjects with pre-existing pIMDs would be of benefit to this population. Subjects with pre-existing pIMDs were not specifically excluded, but subjects had to be healthy enough to participate in a clinical trial, and subjects could not be taking any immunosuppressive medication.

The most recent pre-defined list of pIMDs, updated on 30 June 2017, is provided in Appendix Table 2. Section 7.2.2 provides details on the methodology used for the collection of pIMDs.An overview of the incidence of all pIMDs and pIMDs considered related to vaccination by the investigator by time period, overall and by age stratum in the TVC, is presented in Table 25.

pIMDs were reported at comparable rates regardless of treatment group and age stratum in all time periods analyzed. From the first administered dose up to 30 days post last vaccination, pIMDs were reported by 30 subjects (0.2%) in both groups, while up to 365 days post last vaccination, pIMDs were reported by 90 subjects (0.6%) in the HZ/su group and 105 subjects (0.7%) in the Placebo group. Approximately half of the pIMDs vaccination follow-up period, pIMDs were reported by 179 subjects (1.2%) and 202 subjects (1.4%), respectively.

During the entire post-vaccination follow-up period, pIMDs considered related to vaccination by the investigator were reported by 16 subjects (0.1%) in the HZ/su group and by 18 subjects (0.1%) in the Placebo group.

By PT, the most frequently reported pIMDs in HZ/su and Placebo in all age strata were polymyalgia rheumatica, rheumatoid arthritis, psoriasis and autoimmune thyroiditis. These diseases are known to occur more frequently in the target population of adults ≥50 YOA. Polymyalgia rheumatica develops in patients ≥50 YOA and it is a common medical condition amongst the aging populations of the Western society [Nesher, 2016;

Rooney, 2015]. Epidemiological studies reported an annual incidence of polymyalgia rheumatica between 3.15 and 113 per 100,000 population ≥50 YOA [Barraclough, 2008; Pamuk, 2009; Doran, 2002]. As expected, annual incidence rates increased with h advancing age, from 10.8 per 100,000 population 50-59 YOA to a maximum of 137.1 per 100,000 population 70-79 YOA [Doran, 2002]. Rheumatoid arthritis affects about 1% of the adult population worldwide and can occur in all ethnic groups [Lee, 2001; Cooper, 2003]. Two studies conducted in the US reported annual incidence rates of 63.3 to 89.2 and 69.5 to 107.3 per 100,000 population 55-64 YOA and 75-84 YOA, respectively [Doran, 2002; Myasoedova, 2010]. Psoriasis is estimated to affect about 2% to 4% of the population in Western countries [Gelfand, 2005; Kurd, 2009; Stern, 2004]. The overall incidence rate for psoriasis in adults ≥50 YOA ranged between 69 and 280 per 100,000 person-years [Khalid, 2013; Keller, 2013] and between 78.9 and 321 per 100,000 population [Icen, 2009; Vena, 2010]. For autoimmune thyroiditis, 3 studies reported a peak in the incidence rate at 50-59 YOA of 23 to 57 per 100,000 population [Abraham-Nordling, 2011; Nyström, 2013; Lantz, 2009] and one study reported an incidence of 50 per 100,000 person-years at 60-69 YOA [Carlé, 2011].

Table 25 Main safety pooling analysis: Percentage of subjects reporting the occurrence of at least one pIMD by time period, overall and by age stratum (TVC)

	50-69 YOA								≥70 YOA								Overall							
	HZ/su N= 5887				Placebo N= 5887				HZ/su N= 8758				Placebo N= 8773				HZ/su N=14645				Placebo N=14660			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
Time period	**N**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**	**n**	**%**	**LL**	**UL**
All pIMDs																								
≤30 days post last vaccination	13	**0.2**	0.1	0.4	14	**0.2**	0.1	0.4	17	**0.2**	0.1	0.3	16	**0.2**	0.1	0.3	30	**0.2**	0.1	0.3	30	**0.2**	0.1	0.3
≤365 days post last vaccination	33	**0.6**	0.4	0.8	44	**0.7**	0.5	1.0	57	**0.7**	0.5	0.8	61	**0.7**	0.5	0.9	90	**0.6**	0.5	0.8	105	**0.7**	0.6	0.9
Entire post-vaccination follow-up period	69	**1.2**	0.9	1.5	84	**1.4**	1.1	1.8	110	**1.3**	1.0	1.5	118	**1.3**	1.1	1.6	179	**1.2**	1.1	1.4	202	**1.4**	1.2	1.6
pIMDs considered related to vaccination by the investigator																								
Entire post-vaccination follow-up period	8	**0.1**	0.1	0.3	10	**0.2**	0.1	0.3	8	**0.1**	0.0	0.2	8	**0.1**	0.0	0.2	16	**0.1**	0.1	0.2	18	**0.1**	0.1	0.2

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

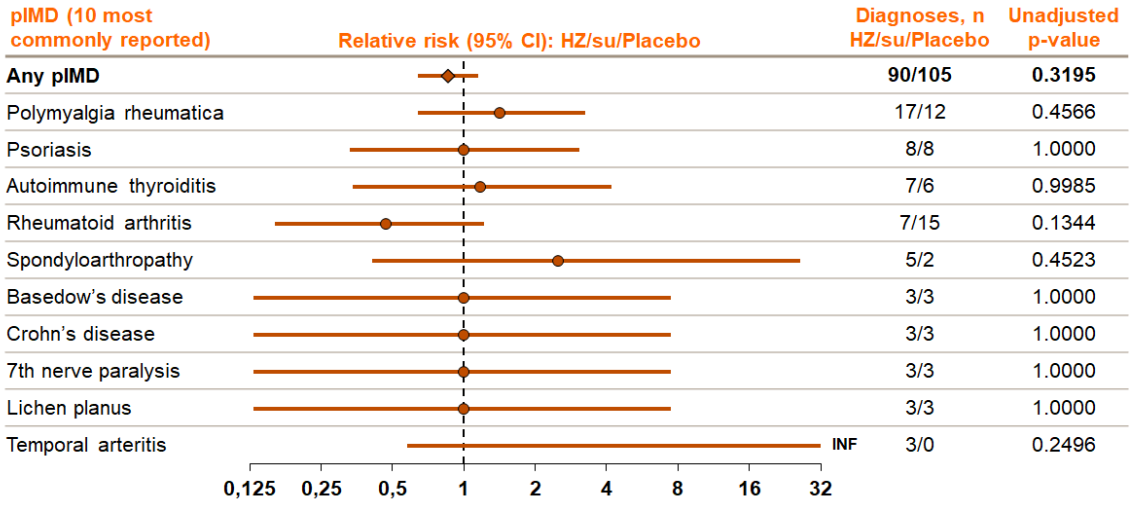
No statistically significant imbalances between the HZ/su and Placebo group have been observed in terms of the overall incidence of pIMDs reported from the first administered dose up to 365 days post last vaccination, i.e., respectively 0.6% (95% CI: 0.5, 0.8) and 0.7% (95% CI: 0.6, 0.9) (RR = 0.86 [95% CI: 0.64, 1.15], unadjusted p-value = 0.3195).

Figure 17 is a forest plot, presenting the results of the comparative analysis for the 10 most frequently reported pIMDs in ≥3 subjects in the HZ/su group by PT, from the first administered dose up to 365 days post last vaccination. This plot shows the point estimate of the RR including the 95% CI.

There were no statistically significant differences (unadjusted p-value <0.05) in the incidence of the 10 most frequently reported pIMDs (≥3 subjects in the HZ/su group by PT) between the HZ/su and Placebo group, with the 95% CI of the RR including the value of 1 for all pIMDs. In addition, for all other PTs reported by <3 subjects in the HZ/su group, there were also no statistically significant imbalances between the groups. Overall, there were no medically meaningful differences in terms of incidence and nature of pIMDs reported in the HZ/su group compared to the Placebo group.

Based on the above data, the medical assessment of individual cases and the literature review, no safety concerns have been identified in terms of pIMDs. However, GSK plans to continue monitoring any safety information about these events of interest in the enhanced and active surveillance activities proposed in Section 8, including potentially serious inflammation-based pathology associated to some of these diseases. In this regard, and of particular interest in people ≥50 YOA, polymyalgia rheumatica with large vessel involvement, temporal arteritis or Giant Cell Arteritis as one of the most aggressive forms of systemic acute inflammatory vasculitis, which can lead to extensive organ ischemia and other complications [Mahr, 2017; Nesher, 2016; Cho, 2017] will be addressed in the planned Targeted Safety Study (TSS).

Figure 17 Main safety pooling analysis: Relative Risk between groups of subjects reporting the occurrence of the 10 most frequently reported pIMDs (≥3 subjects in HZ/su group) by MedDRA PT, from first vaccination up to 365 days post last vaccination (TVC)



INF: infinity

An additional analysis was performed on subjects vaccinated in ZOSTER-006 and ZOSTER-022 and who were identified as having pIMDs reported in the medical history at study inclusion. This search was conducted by querying the global medical history of the subjects included in the TVC with a customized MedDRA query for pIMDs [Tavares, 2013]. The search identified 983 subjects in the HZ/su group and 960 subjects in the Placebo group who presented with pre-existing pIMDs prior to vaccination. The disease events most frequently present at baseline were psoriasis (21.9% and 24.9%, respectively), spondyloarthropathy (11.1% and 9.3%, respectively) and rheumatoid arthritis (9.8% in both groups) (Table 26). Of these subjects with pre-existing pIMDs, 27 subjects (2.8%) in HZ/su group and 27 subjects (2.8%) in Placebo group presented with a possible exacerbation/worsening of the pre-existing pIMD as per investigator assessment, and respectively 16 subjects (1.6%) and 23 subjects (2.4%) reported a new onset of a different pIMD during the entire post-vaccination follow-up period. The majority of the subjects who reported a pIMD in the past medical history did neither experience a possible exacerbation of their pre-existing disease as per investigator assessment, nor a new onset of a different pIMD during the entire post-vaccination follow-up period (97.6% in the HZ/su group and 97.8% in the Placebo group). The numbers were balanced between the groups (Table 27).

Overall, based on the data generated to date, there is no evidence of exacerbation of pre-existing pIMDs or new onset of pIMDs after vaccination.

Table 26 Main safety pooling analysis: Percentage of subjects reporting the occurrence of the 10 most frequently reported pre-existing pIMDs prior to vaccination (≥3.0% in HZ/su group), classified by MedDRA Primary SOC and PT (TVC with pre-existing pIMDs)

		HZ/su N = 983				Placebo N = 960			
				95% CI				95% CI	
Primary System Organ Class (CODE)	Preferred Term (CODE)	n	%	LL	UL	n	%	LL	UL
Gastrointestinal disorders (10017947)	Coeliac disease (10009839)	41	**4.2**	3.0	5.6	34	**3.5**	2.5	4.9
	Colitis ulcerative (10009900)	31	**3.2**	2.2	4.4	30	**3.1**	2.1	4.4
Metabolism and nutrition disorders (10027433)	Type 1 diabetes mellitus (10067584)	31	**3.2**	2.2	4.4	36	**3.8**	2.6	5.2
Musculoskeletal and connective tissue disorders (10028395)	Polymyalgia rheumatica (10036099)	36	**3.7**	2.6	5.0	37	**3.9**	2.7	5.3
	Rheumatoid arthritis (10039073)	96	**9.8**	8.0	11.8	94	**9.8**	8.0	11.8
	Spondyloarthropathy (10051265)	109	**11.1**	9.2	13.2	89	**9.3**	7.5	11.3
Nervous system disorders (10029205)	VIIth nerve paralysis (10050040)	36	**3.7**	2.6	5.0	32	**3.3**	2.3	4.7
Skin and subcutaneous tissue disorders (10040785)	Lichen planus (10024429)	33	**3.4**	2.3	4.7	24	**2.5**	1.6	3.7
	Psoriasis (10037153)	215	**21.9**	19.3	24.6	239	**24.9**	22.2	27.8
	Vitiligo (10047642)	37	**3.8**	2.7	5.2	33	**3.4**	2.4	4.8

N = number of subjects with at least one administered dose
n/% = number/percentage of subjects reporting the symptom at least once
95% CI = exact 95% confidence interval; LL = Lower Limit, UL = Upper Limit

Table 27 Main safety pooling analysis: Number and percentage of subjects with pre-existing pIMDs and its evolution after vaccination (TVC with pre-existing pIMDs)

	HZ/su N = 983		Placebo N = 960	
	n	%	n	%
Subjects with a possible exacerbation of at least one pIMD after vaccination	27	**2.8**	27	**2.8**
Subjects with at least one pIMDs with no exacerbation after vaccination	959	**97.6**	939	**97.8**
Subjects with at least one new onset of a different pIMD during the entire post-vaccination follow-up period	16	**1.6**	23	**2.4**

N = Number of subjects with pre-existing pIMDs
n/% = Number/percentage of subjects with at least one event
% = n/N * 100
Note that one subject may have reported one or more pIMDs at baseline

7.4.5.2. Gout

Following an assessment of risks of inflammation after exposure to HZ/su, a numerical imbalance in the reporting rate of gout (including gouty arthritis) as unsolicited AE was identified for which a biologically plausible relationship with vaccination cannot be excluded at this point.

Gout is a chronic disease of deposition of monosodium urate crystals in joints [Dalbeth, 2016]. There are several genetic and non-genetic factors that can contribute to the progression to gout condition. The biological precursor to gout is elevated serum uric acid concentration, but asymptomatic hyperuricemia is common and does not necessarily progress to clinical gout, as other risk factors are involved. Production of uric acid resulting from purine metabolism is a physiological and expected consequence of inflammation because it is locally released by dying cells such as neutrophils during resolution of inflammation [Jounai, 2013; Mandal, 2015]. The mode of action of HZ/su requires a local and transient inflammatory response for the observed benefit. However, non-clinical/clinical studies have not been performed confirming or disproving that local inflammation may result in a transient increase of uric acid in the circulation. Therefore, if uric acid serum levels are somehow connected to gout, biological plausibility of the observed imbalance cannot be excluded at this point. However, there is currently no biological evidence to support causality between HZ/su and the event of gout. This is further confounded by the fact that multiple alternative factors can intervene in the pathophysiologic mechanism of gout and by the lack of a linear relationship between uric acid concentrations in serum and progression to gout.

In the main safety pooling within the 30-day post-vaccination period, at least one unsolicited AE of gout or gouty arthritis was experienced by 27 subjects (0.2% [95% CI: 0.1, 0.3]) in the HZ/su group and 8 subjects (0.1% [95% CI: 0.0, 0.1]) in the Placebo group (RR = 3.4 [95% CI: 1.5, 8.6]; unadjusted p-value <0.01). Most of these events were non-serious and the vast majority of these subjects had either previous episodes of gout reported in the past medical history or concurrent medical conditions that are known risk factors for developing gout (i.e., diabetes, hypertension, hypercholesterolemia, alcohol or tobacco consumption, obesity) and may have contributed to the occurrence of the reported episode.

From first vaccination up to 365 days post vaccination, SAEs associated with gout or gouty arthritis were reported by 5 subjects (<0.05%) in the HZ/su group and 1 subject (<0.05%) in the Placebo group (RR = 5.0 [95%CI: 0.6, 236.7]; unadjusted p-value = 0.22). All these SAEs revealed alternative explanations for their occurrence.

Based on the observed numerical imbalance of these events in the clinical data and on the fact that biological plausibility of the observed imbalance cannot be excluded at this point, GSK considers the event of gout to be an AE of interest. In the post-licensure setting of HZ/su, GSK plans to monitor any safety information about gout and gouty arthritis through the active safety surveillance activities proposed in the Pharmacovigilance Plan (see Section 8).

7.4.5.3. Anaphylaxis

In order to retrieve any potential cases featuring anaphylaxis, a search was performed using the SMQ "Anaphylactic reaction, narrow" (MedDRA v.18.0 SMQ). This search was performed in the TVC of the main safety pooling, and searched for cases reported as unsolicited (non-serious and serious) AEs within the 30-day post vaccination period. Retrieved cases of anaphylaxis were assessed using the "anaphylaxis case definition and guidelines" described by the Brighton Collaboration Anaphylaxis Working Group [Rüggeberg, 2007].

Under the SMQ "Anaphylactic reaction, narrow" in the main safety pooling analysis during the 30-day post-vaccination period, 1 subject in the HZ/su group reported a non-serious AE of 'anaphylactic reaction' at Day 0 (after Dose 1), which was grade 1 in severity and considered related to HZ/su vaccination by the investigator. This case was assessed by GSK as anaphylaxis level 5 (i.e., not a case of anaphylaxis) according to the Brighton collaboration case definition. The subject presented AEs of injection site pain, pyrexia, fatigue, injection site erythema, chills, nausea and disorientation. All of these AEs recovered at Day 3 without medical attendance or treatment.

Overall, no cases of HZ/su-related anaphylaxis were identified in any subject vaccinated with HZ/su in all studies included in the BLA.

7.4.5.4. AEs leading to withdrawal from the study

The compliance to the two-dose schedule was >95% in both groups. Up to 1 month post Dose 2 (Month 3), more subjects in the HZ/su group compared to the Placebo group were withdrawn from the study due to a non-serious AE (0.4% and 0.1%, respectively), which was also observed during the entire post-vaccination follow-up period (0.5% and 0.2%, respectively). In contrast, a similar number of subjects in both groups were withdrawn due to an SAE during both time periods (respectively 0.4% and 0.3% up to Month 3 and 4.7% and 4.9% during the entire study period) (Table 28).

Table 28 Main safety pooling analysis: Number of subjects vaccinated and withdrawn due to an (S)AE (TVC)

	Up to 1 month post Dose 2 (Month 3)				During the entire post-vaccination follow-up period			
	HZ/su N=14645		Placebo N=14660		HZ/su N=14645		Placebo N=14660	
	n	%	n	%	n	%	n	%
Subjects who discontinued treatment due to an (S)AE	116	0.8	65	0.4	760	5.2	755	5.2
Non-Serious AE	62	0.4	17	0.1	77	0.5	33	0.2
SAE	54	0.4	48	0.3	683	4.7	722	4.9

Vaccinated = number of subjects who were vaccinated in the study
Withdrawn = number of subjects who withdrew from the study before Month 3 visit

7.4.6. Analysis of Adverse Events in the Main Safety Pooling by Race, Ethnicity and Gender

In addition to the overall analyses in the main safety pooling, subgroup analyses have been performed in the TVC of the main safety pooling by race, ethnicity and gender. For all 3 subgroups, analyses have also been performed by age for the strata 50-59 YOA, 60-69 YOA and ≥70 YOA. Overall, the conclusions of the subgroup analyses by race, ethnicity and gender in the main safety pooling are consistent with conclusions of the overall analysis described in Section 7.4. Based on the review of available safety data, no safety concerns have been identified.

7.5. Analysis of Adverse Events in the Main Safety Pooling in North American Subjects

In addition to the analyses in the main safety pooling for all subjects, analyses have also been performed for North American subjects in the main safety pooling. The reactogenicity and safety profile of HZ/su in North American subjects from the main safety pooling were comparable with the safety profile in the overall population. There were no additional safety concerns with regards to SAEs, fatal SAEs and pIMDs in North American subjects, for which the incidence was similar in the HZ/su and Placebo groups.

Of note, unsolicited AEs with an incidence ≥1.0% in HZ/su recipients, and at least 2-fold higher than in the Placebo group in the TVC for North American subjects included the expected local and general symptoms observed in the TVC for the overall population, except for influenza-like illness (1.0% and 0.3% in the HZ/su and Placebo groups, respectively in North American subjects, and 0.8% and 0.3%, respectively in the overall population).

Based on the review of available safety data, no safety concerns have been identified.

7.6. Other Safety Aspects

Overall, the safety results from all individual studies not included in the main safety pooling were consistent with those from the main safety pooling. Safety data available from the CDP with HZ/su in the target population of adults ≥ 50 YOA have not raised any safety concerns.

Section 7.6.1 provides an overview of fatal SAEs and Section 7.6.2 of HZ cases reported in each study included in the BLA and discussed in this briefing document. Sections 7.6.3 to 7.6.6 summarize the safety results from 4 individual studies in adults ≥50 YOA not included in the safety pooling analyses: ZOSTER-026 (other vaccination schedules), ZOSTER-004 (co-administration with FLU-D-QIV), ZOSTER-033 (subjects with previous HZ) and ZOSTER-007 (lot-to-lot consistency). Section 7.6.7 provides a summary of the safety of HZ/su in a limited number of adults ≥18 YOA with IC conditions.

7.6.1. Fatal Serious Adverse Events and Potential Immune-Mediated Diseases Reported in the BLA

For completeness, Table 29 provides an overview of the number of subjects who reported fatal SAEs and pIMDs during the entire study period of the 12 studies included in the BLA and discussed in this briefing document. These data do not alter the conclusions made on the basis of the safety data of the main safety pooling analysis (ZOSTER-006 and ZOSTER-022).

At least one fatal SAE was reported by 650 subjects receiving HZ/su and 694 subjects receiving another vaccine, of which 97.5% and 98.0%, respectively were reported in the studies from the main safety pooling (ZOSTER-006 and ZOSTER-022), while in the remaining 10 studies, 16 and 14 subjects in the HZ/su and the Placebo groups, respectively, reported fatal SAEs. None of these fatal SAEs were assessed as causality related to vaccination by the investigator.

At least one pIMD was reported by 193 subjects receiving HZ/su and 202 subjects receiving another vaccine. Again, the majority of these cases were reported in the main safety pooling (92.7% and 100%, respectively), while in the other studies, 14 subjects receiving HZ/su reported pIMDs, generally consistent with those from the main safety pooling.

More details on the fatal cases and pIMDs reported in ZOSTER-006 and ZOSTER-022 are presented in Sections 7.4.4 and 7.4.5.1, respectively, while cases from the remaining 10 studies are provided in Table 30 and Table 31, respectively..

Table 29 Overview of subjects reporting fatal SAEs and pIMDs during the entire study period of studies part of the BLA (TVC)

Study	Follow-up time for SAEs/pIMDs post last vaccination	Number of subjects reporting at least one fatal SAE		Number of subjects reporting at least one pIMD	
		HZ/su	Other vaccine	HZ/su	Other vaccine
ZOSTER-006	4.4 years (median/subject)	208	221	87	105
ZOSTER-022	4.2 years (median/subject)	426	459	92	97
ZOSTER-004	12 months	7	1	6	0
ZOSTER-007	1 month*	1	NA	6	NA
ZOSTER-026	12 months	2	NA	0	NA
ZOSTER-003	1 month	0	2	0	0
ZOSTER-011	10 months	0	1	0	0
ZOSTER-012	22 months	3	8	0	0
ZOSTER-013	34 months	0	0	0	0
ZOSTER-024	70 months	2	0	2	0
ZOSTER-010	12 months	1	2	0	0
ZOSTER-033	12 months	0	0	0	0
TOTAL		**650**	**694**	**193**	**202**

NA = not applicable
* Only data up to 1 month post last vaccination (Month 3) were available at the time of submission of the BLA and presented here. The entire study duration was 12 months post last vaccination.

Table 30 Listing of fatal SAEs reported during the entire study period of studies part of the BLA, excluding ZOSTER-006 and ZOSTER-022 (TVC)

Study	Study group[a]	Age at onset (Year)	Preferred Term	Dose	Day of onset	Duration	Intensity
ZOSTER-004[b]	Co-Ad	72	Cerebrovascular disorder	2	91	1	3
	Co-Ad	75	Urosepsis	2	142	37	3
	Co-Ad	86	Pneumonia	2	300	35	3
			Respiratory failure	2	334	1	3
	Control	79	Hepatic cancer	3	95	45	3
			Pancreatic carcinoma	3	95	45	3
	Control[c]	75	Hepatic cancer metastatic	1	17	16	3
	Control	58	Death	3	195	[(b)]	3
	Control	78	Death	3	94	[(b)]	3
	Control	68	Cardiac failure congestive	3	234	19	3
ZOSTER-007[d]	HZ/su Lot A	77	Acute myocardial infarction	1	23	8	3
ZOSTER-026	HZ/su, 0, 2-month schedule	79	Cerebral haemorrhage	2	363	2	3
	HZ/su, 0, 12-month schedule	77	Cardiovascular disorder	1	246	1	3
ZOSTER-003	gE1001B	75	Drowning	1	17	[(b)]	-
	S gE1B	71	Bronchial carcinoma	1	32	190	-
ZOSTER-011	S gE1B	75	Diabetic gangrene	2	111	119	3

Study	Study group[a]	Age at onset (Year)	Preferred Term	Dose	Day of onset	Duration	Intensity
ZOSTER-012	gE251B	80	Peripheral arterial occlusive disease	2	1010	41	2
	gE251B	82	Lung neoplasm malignant	2	568	154	3
	HZ/su	78	Metastases to bone	2	295	499	3
			Metastases to liver	2	295	499	3
	HZ/su	64	Hypopharyngeal cancer stage III	2	508	261	3
	HZ/su	78	Sudden death	2	881	[b]	5
	gE 1001B	76	Pancreatic carcinoma metastatic	2	816	75	3
	gE 1001B	77	Amyloidosis	2	854	148	3
	S gE1B	79	Transitional cell carcinoma	2	756	259	3
	S gE1B	87	Myocardial infarction	2	888	1	3
	S gE1B	73	Squamous cell carcinoma	2	542	358	3
	gE100S	83	Peptic ulcer perforation	2	555	21	3
ZOSTER-024	HZ/su	80	Circulatory collapse	2	1438	1	3
	HZ/su	85	Death	2	1698	[b]	3
ZOSTER-010	HZ/su	69	Myocardial infarction	1	50	1	3
	gE/Saline	82	Cardiac failure	2	182	1	3
	gE/Saline	71	Acute myocardial infarction	2	284	29	3
			Renal failure	2	285	28	3

[a] Refer to Appendix Table 1 for details regarding the study groups.
[b] Subjects in the Co-Ad group received 2 doses of HZ/su at Month 0 and 2, and 1 dose of FLU-D-QIV at Month 0; subjects in the Control group received 1 dose of FLU-D-QIV at Month 0, and 2 doses of HZ/su at Months 2 and 4.
[c] The subject only received one dose of FLU-D-QIV and no doses of HZ/su.
[d] Only cases reported up to 1 month post Dose 2 (Month 3)

Table 31 Listing of pIMDs reported during the entire study period of studies part of the BLA, excluding ZOSTER-006 and ZOSTER-022 (TVC)

Study	Study group	Age at onset (Year)	Preferred Term	Dose	Day of onset	Relation as per investigator	SAE (Y/N)	Outcome
ZOSTER-004[a]	Co-Ad	67	Myasthenia gravis	2	112	N	Y	Not recovered/ not resolved
	Co-Ad	70	VIIth nerve paralysis	2	322	N	N	Recovering/ resolving
	Co-Ad	72	Psoriasis	2	70	N	N	Not recovered/ not resolved
	Co-Ad	55	Rheumatoid arthritis	2	202	N	Y	Not recovered/ not resolved
	Control	69	Vocal cord paralysis	3	268	N	N	Not recovered/ not resolved
	Control	70	Colitis ulcerative	2	5	N	Y	Recovered/ resolved
ZOSTER-007[b]	HZ/su Lot A	54	Raynaud's phenomenon	2	16	Y	N	Recovered/ resolved
	HZ/su Lot A	74	Polymyalgia rheumatica	1	44	Y	N	Recovering/ resolving
	HZ/su Lot A	76	Psoriatic arthropathy	2	79	N	N	Not recovered/ not resolved
	HZ/su Lot A	70	Pulmonary fibrosis	1	6	N	N	Not recovered/ not resolved

Study	Study group	Age at onset (Year)	Preferred Term	Dose	Day of onset	Relation as per investigator	SAE (Y/N)	Outcome
ZOSTER-007 *(continued)*	HZ/su Lot C	73	Spondyloarthro-pathy	1	15	N	N	Not recovered/ not resolved
	HZ/su Lot C	57	Rheumatoid arthritis[c]	2	62	N	N	Recovering/ resolving
ZOSTER-024	HZ/su	79	Polymyalgia rheumatica	2	1526	N	N	Not recovered/ not resolved
	HZ/su	87	Crohn's disease	2	2096	N	Y	Recovered/ resolved

[a] Subjects in the Co-Ad group received 2 doses of HZ/su at Month 0 and 2, and 1 dose of FLU-D-QIV at Month 0; subjects in the Control group received 1 dose of FLU-D-QIV at Month 0, and 2 doses of HZ/su at Months 2 and 4.
[b] Only cases reported up to 1 month post Dose 2 (Month 3)
[c] This non-serious case of rheumatoid arthritis was initially reported as vaccine-related by the investigator at Month 3 but was upon follow-up no longer considered to be vaccine-related by the investigator at study end.

7.6.2. Herpes Zoster Cases Reported in the BLA

7.6.2.1. ZOSTER-006 and ZOSTER-022 breakthrough cases

As a consequence of the high VE against HZ, a low number of breakthrough cases, i.e., confirmed HZ cases that occurred in the HZ/su group during the entire ZOSTER-006 and ZOSTER-022 study period of the mTVC, were accrued. There were 9 HZ breakthrough cases in ZOSTER-006 and 23 HZ breakthrough cases in ZOSTER-022. All HZ cases were seen by a physician. Five of the breakthrough cases in ZOSTER-022 were associated with HZ-related complications, including 4 cases of PHN and one case with an ophthalmic complication (blurred vision). Of the 32 breakthrough cases, 26 were PCR-confirmed, while 25 cases were confirmed to be zoster by HZAC. There were 2 cases without a PCR sample and 4 cases for which the PCR result was undetermined, with all 6 confirmed to be zoster by HZAC. A brief description of all HZ breakthrough cases is provided in Appendix Table 3. These breakthrough cases did not show any specific common pattern such as clinical presentation or underlying medical conditions.

7.6.2.2. Suspected HZ cases in other studies

Across the 10 studies which were part of the BLA and discussed in this document (excluding studies ZOSTER-006 and ZOSTER-022, for which cases were described in Section 7.6.2.1), clinically suspected cases of HZ were reported by 11 subjects receiving HZ/su and by 9 subjects receiving another vaccine. A short description of the reported cases in subjects receiving HZ/su is provided below. Of note, no laboratory confirmation of these cases was required per protocol, and some suspected cases were based on self-reporting by the subjects.

In ZOSTER-004, 1 subject in the Co-Ad group reported a suspected HZ infection 238 days after study start. The event was clinically diagnosed and relevant information was collected from the subject by phone by the investigator. The event was of moderate intensity and resolved.

In ZOSTER-007, 1 subject in group HZ/su Lot C was clinically diagnosed with HZ infection of moderate intensity that began 4 days post Dose 2 and resolved after 31 days. This case was assessed as related to vaccination by the investigator.

In ZOSTER-024, between Month 36 and Month 72, 1 subject in the HZ/su group reported a painful localized rash on the left femur about 5 years and 9 months post last vaccination assessed as not related to vaccination by the investigator.

In ZOSTER-033, there were 9 episodes of suspected HZ reported in 6 subjects during this study. Details regarding these cases are provided in Section 7.6.5.

7.6.3. Safety of HZ/su When Administered According to Other Vaccination Schedules (ZOSTER-026)

In ZOSTER-026, the safety and reactogenicity of the use of HZ/su according to different vaccination schedules was evaluated in adults ≥50 YOA, i.e., at either 0, 2; 0, 6 or 0, 12 months.

At least one solicited symptom (local or general) during the 7-day post-vaccination period was reported by 89.9%, 89.1% and 92.2% of subjects on a , 0, 2-month, 0, 6-month and 0,12-month schedule, respectively. The most frequently reported solicited local symptom was pain, reported by 76.5%, 79.8% and 84.5% of subjects, respectively. Pain was also the most frequently reported grade 3 solicited local symptom (5.9%, 5.0% and 10.3% of subjects, respectively). The most frequently reported solicited general symptoms were fatigue (45.4%, 52.9% and 61.2% of subjects, respectively), myalgia (52.9%, 47.9% and 55.2%, respectively), headache (39.5%, 39.5% and 45.7%, respectively) and shivering (31.1%, 29.4% and 41.4%, respectively). Grade 3 solicited general symptoms were reported by ≤5.9% of subjects for any given symptom.

At least one unsolicited symptom within the 30-day post-vaccination period was reported by 22.7%, 22.7% and 19.8% of subjects on a , 0, 2-month, 0, 6-month and 0,12-month schedule, respectively.

During the entire study period (up to 12 months post last vaccination), SAEs (fatal and non-fatal) were reported by 26 subjects (5 subjects on a , 0, 2-month schedule, 9 subjects on a 0, 6-month schedule and 12 subjects on a 0,12-month schedule). Two subjects died due to SAEs, reported 1 year and 8 months post last vaccination (cerebral hemorrhage and cardiovascular disorder). None of these SAEs were considered related to vaccination by the investigator. No pIMDs were reported during the entire study period.

The overall safety profile of HZ/su was similar between subjects vaccinated following a 0, 6 month and 0, 12 month schedule and subjects vaccinated following a 0, 2 month schedule.

7.6.4. Safety of HZ/su When Co-administered With Other Vaccines: FLU-D-QIV Co-administration (ZOSTER-004)

In ZOSTER-004, the safety and reactogenicity of HZ/su was evaluated in adults ≥50 YOA having received HZ/su concomitantly (Co-Ad group) or sequentially (Control

group) with the seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine (FLU-D-QIV).

At least one solicited symptom (local or general) during the 7-day post-vaccination period was reported by 89.8% of subjects in the Co-Ad group and 88.4% of subjects in the Control group. The most frequently reported solicited local symptom was pain, reported by 83.7% and 77.0%, respectively. Pain was also the most frequently reported grade 3 solicited local symptom (13.4% and 9.7%, respectively). The most frequently reported solicited general symptoms were fatigue (54.5% and 45.0%, respectively), myalgia (48.9% and 48.7%, respectively), headache (44.5% and 41.2%, respectively), shivering (42.3% and 43.8%, respectively) and arthralgia (37.5% and 32.7%, respectively). Grade 3 solicited general symptoms were reported by ≤9.2% of subjects for any given symptom.

At least one unsolicited AE within the 30-day post-vaccination period was reported by 26.6% of subjects in the Co-Ad group (vaccinations at Months 0 and 2), and 39.0% of subjects in the Control group (vaccinations at Month 0, 2 and 4.

Note that when HZ/su and FLU-D-QIV were concomitantly administered, each vaccine was administered at different injection sites. This allowed evaluation of solicited local symptoms for each vaccine separately. Co-administration of HZ/su did not impact the reactogenicity profile of FLU-D-QIV and vice versa.

During the entire post-vaccination follow-up period (12 months post last vaccination), non-fatal SAEs were reported by 39 subjects (9.4%) in the Co-Ad group and 34 subjects (8.2%) in the Control group. The most common SAEs reported in ≤3 subjects per group were coronary artery disease, pneumonia, cerebrovascular accident and osteoarthritis. Fatal events were reported for 8 subjects, of which 3 were in the Co-ad group and 5 were in the Control group. All of these fatal events except one occurred more than 90 days post last dose. In one case, the subject experienced a fatal event (worsening of metastatic hepatocellular cancer) [redacted] days post Dose 1. None of the fatal and non-fatal SAEs were assessed to be causally related to vaccination by the investigator.

During the entire post-vaccination follow-up period, pIMDs were reported by 4 subjects (1.0%) in the Co-Ad group and 2 subjects (0.5%) in the Control group. None of these events were considered related to vaccination by the investigator.

The safety results of ZOSTER-004 indicate that HZ/su has an overall clinically acceptable safety profile when co-administered with a seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine, and safety results were in line with what has been observed across studies when HZ/su has been administered without co-administered vaccine.

7.6.5. Safety of HZ/su in Subjects with Previous Herpes Zoster (ZOSTER-033)

In ZOSTER-033, the safety and reactogenicity of HZ/su was evaluated in adults ≥50 YOA with a history of HZ. The safety profile was found to be clinically acceptable and no safety concerns were identified.

At least one solicited symptom (local or general) during the 7-day post-vaccination period was reported by 81.1% of subjects. The most frequently reported solicited local symptom was pain, reported by 73.7% of subjects, with 8.4% of subjects reporting grade 3 pain. The most frequently reported solicited general symptoms were fatigue, headache, myalgia and shivering, reported by 60.0%, 38.9%, 36.8% and 32.6% of subjects, respectively. Grade 3 solicited general symptoms were reported by ≤ 10.5% of subjects for any given symptom.

At least one unsolicited symptom within the 30-day post-vaccination period was reported by 31.3% of subjects.

During the entire study period (up to 12 months post last vaccination), non-fatal SAEs were reported by 3 subjects (3.1%), all of which were considered not related to vaccination by the investigator. One subject had SAEs (exacerbation of chronic gastritis and gastroesophageal reflux disease) reported within 30 days post last vaccination while beyond these 30 days, 1 subject reported perforated duodenal peptic ulcer and another subject reported cholelithiasis with cholecystitis and pancreatitis.

No fatal SAEs or pIMDs were reported during the entire study period.

Although no control group was included in this study, the safety profile was generally similar to that observed in other clinical studies in a population with no history of HZ.

There were 9 episodes of suspected HZ reported in 6 subjects (6.3%) during this study. An overview of these suspected HZ cases is provided in Table 32. Study participants were trained to recognize and report symptoms of HZ during the initial visit, which may have contributed to an increased awareness of signs potentially associated with HZ, and leading to an increased reporting of non-HZ symptoms as suspected HZ. This over-reporting is suspected, especially in the context of the high HZ VE shown in adults ≥50 YOA (see Section 5.2.2.1). Note that none of these suspected HZ cases were considered related to vaccination by the investigator.

As the study was not designed to formally evaluate HZ recurrence (uncontrolled study with a limited sample size and no HZ confirmatory testing), conclusions regarding this aspect of the study have to be considered with caution, in particular since some cases were self-reported. However, in order to further assess the safety and immunogenicity of HZ/su in persons with previous HZ, GSK is planning to conduct a second study in this population. This study would be a randomized, observer-blind, placebo-controlled study to assess the safety, reactogenicity and immunogenicity of HZ/su in subjects ≥50 YOA with a history of HZ. Suspected HZ cases that would arise in the study will be confirmed either by PCR or by an HZAC. The final design of the study is under discussion with regulatory authorities.

Table 32 Overview of suspected HZ episodes reported during ZOSTER-033

Subgroup	Subject no.	Previous dose	Day onset	Duration	AE description	Medical advice	Medically attended visit	Intensity	Causality	Outcome
60-69 YOA	1	2	288	12	Herpes Zoster	N	None	Mild	N	Recovered/resolved
	18	2	131	8	Shingles	N	None	Mild	N	Recovered/resolved
	114	1	178	15	Herpes Zoster of neck and posterior occipital pain	Y	Medical personnel	Mild	N	Recovered/resolved
≥ 70 YOA	13	2	178	9	Herpes zoster left ear and head - Small Erythematous rash behind left ear	Y	Medical personnel	Moderate	N	Recovered/resolved
			204	14	Herpes Zoster	Y	Medical personnel	Moderate	N	Recovered/resolved
	20	1	56	31	Right Flank - Herpes z**oster**	Y	Medical personnel	Moderate	N	Recovered/resolved
	106	1	28	5	Herpes zoster left back	N	None	Mild	N	Recovered/resolved
			54	193	Herpes zoster left back	N	None	Mild	N	Recovered/resolved
			430	Ongoing	Herpes Zoster Left Side Back	N	None	Mild	N	Not recovered/ Not resolved

7.6.6. Safety Profile in Relation to the Lot-to-lot Consistency (ZOSTER-007)

In ZOSTER-007, the safety and reactogenicity of 3 lots of HZ/su was evaluated in adults ≥50 YOA. As safety data up to 1 year post last vaccination were not yet available at the time of preparation of the BLA, safety results up to Month 3 are presented below.

At least one solicited symptom (local or general) during the 7-day post-vaccination period was reported by 92.2%, 92.2% and 90.3% of subjects in the HZ/su Lot A, Lot B and Lot C groups, respectively. Pain was the most frequently reported solicited local symptom, reported by 86.6%, 90.3% and 86.0% of subjects, respectively. The most frequently reported solicited general symptoms were myalgia (52.3% to 59.0% of subjects), fatigue (49.5% to 52.5%) and headache (41.2% to 49.8%). Grade 3 solicited general symptoms were reported by ≤ 11.1% of subjects for any given symptom.

At least one unsolicited symptom within the 30-day post-vaccination period was reported by 33.0%, 30.4% and 34.7% of subjects in the HZ/su Lot A, Lot B and Lot C groups, respectively.

SAEs (fatal and non-fatal) were reported by 9 out of 218 subjects (4.1%) in group HZ/su Lot A (including 1 fatal SAE), 9 out of 217 subjects (4.1%) in group HZ/su Lot B and 11 out of 216 subjects (5.1%) in group HZ/su Lot C, and none of these SAEs were considered by the investigator as related to vaccination.

pIMDs were reported by 5 subjects (2.3%) in Lot A and 3 subjects (1.4%) in Lot C. Three of these pIMDs (Raynaud's phenomenon and polymyalgia rheumatica in Lot A and rheumatoid arthritis in Lot C) were considered related to vaccination by the investigator.

In conclusion, the reactogenicity and safety profile was similar in the 3 clinical HZ/su lots and safety results from ZOSTER-007 support consistency of manufacturing of HZ/su.

7.6.7. Safety of HZ/su in Immunocompromised Subjects

Although IC adults ≥18 YOA are not included in the proposed indication for which approval is sought by this application (see Section 1.1), the safety results of the completed studies ZOSTER-001 and ZOSTER-015 showed that HZ/su was well tolerated when administered to IC adults ≥18 YOA with autologous hematopoietic stem cell transplant or with HIV infection, respectively. Of note, 54% of the study subjects who received at least one dose of HZ/su in these IC studies were ≥50 YOA.

7.7. Conclusions Regarding Safety

The safety data from the studies included in the BLA support the following conclusions:

- The safety profile of HZ/su has been well characterized and demonstrated to be acceptable. The safety conclusions are largely based on data from the main safety pooling analysis, including data from >14,600 subjects from different geographic regions who received HZ/su in the 2 pivotal Phase III studies ZOSTER-006 and ZOSTER-022.
- Solicited local and general symptoms were reported with a higher frequency in the HZ/su group compared to the Placebo group. However, the majority of symptoms were mild to moderate in severity, and self-limited with a median duration of at most 3 days. Furthermore, the compliance with the second vaccine dose was >95% in the HZ/su and Placebo groups of the main safety pooling. The drop-out rate due to (S)AEs was low in both groups.
- The incidence of unsolicited AEs reported from Day 7 through Day 29 was comparable between the groups. The majority of the imbalances in terms of unsolicited AEs between HZ/su and Placebo recipients were mainly related to PTs referring to 'solicited' symptoms reported during the 7-day post-vaccination period by subjects that were part of the 7-day diary card subset.
- The incidence of SAEs, including fatal cases, was similar in the HZ/su and Placebo groups during all follow-up time periods analyzed, with a frequency of ~10% for all SAEs and 0.1% for related SAEs (as per investigator assessment) in each group up to 365 days post last vaccination. The majority of SAEs, including fatal cases, occurred in subjects ≥70 YOA and the majority of fatal SAEs had a time to onset of longer than 1 year post last vaccination.
- The incidence of pIMDs was similar in the HZ/su and Placebo groups during all follow-up time periods analyzed, with a frequency of ~1% for all pIMDs and 0.1% for related pIMDs (as per investigator assessment) in each group during the entire post-vaccination follow-up period. The incidence of pIMDs was balanced between age groups, and approximately half of the pIMDs occurred with time to onset longer than 1 year post last vaccination.
- Specific SAEs and pIMDs reported were as expected for the target population of adults ≥50 YOA.
- Following an assessment of risks of inflammation after exposure to HZ/su, a numerical imbalance in the reporting rate of gout (including gouty arthritis) as unsolicited AE was identified for which a biologically plausible relationship with vaccination cannot be excluded at this point. GSK considers the event of gout to be an AE of interest and plans to include it in the active safety surveillance activities of the proposed Pharmacovigilance Plan.
- No case of HZ/su-related anaphylaxis has been reported in any study included in the BLA. The incidence of major adverse cardiovascular and cerebrovascular events (fatal and non-fatal) was similar in the HZ/su and Placebo groups.

- The reactogenicity and safety profile of HZ/su in North American subjects from the main safety pooling were comparable with the safety profile in the overall population of the main safety pooling.
- The safety results from all other individual studies in adults ≥50 YOA included in the BLA were overall consistent with those from the main safety pooling and revealed no safety concerns.
- HZ/su has an overall clinically acceptable safety profile when co-administered with a seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine (ZOSTER-004).
- HZ/su has shown a clinically acceptable safety profile when administered to a limited number of adults (including 96 subjects ≥50 YOA) with history of HZ (ZOSTER-033). However additional studies are warranted in this population to confirm the safety profile in this population.

8. PHARMACOVIGILANCE PLAN

As part of GSK's approach to pharmacovigilance for HZ/su, a TSS using an adequate data source is under development and the feasibility is being assessed to evaluate AEs of special interest (e.g., gout). The sample size will be defined by the specific safety endpoints of interest, which will be identified in agreement with regulatory authorities. Potential methodologies for analysis would include observed/expected analysis and assessment of relative and absolute risk (number of excess cases of a given event in the vaccinated population), if a comparator can be identified. In the absence of a comparator, background rates from the literature will be used.

Additional active safety surveillance activities will be conducted to further monitor the safety profile of HZ/su in accordance with the feedback received from FDA. The active surveillance will enable GSK to further enhance the passive surveillance that will continuously be performed for HZ/su, as well for all other licensed vaccines. To this end, GSK is considering using existing demographic, health and vaccination program information and data collection systems in the US, potentially including the Post-licensure Rapid Immunization Safety Monitoring System (PRISM) to monitor AEs after HZ/su vaccination. These AEs will include, but will not be limited to, a pre-defined list of AEs of interest, which will be defined in agreement with regulatory authorities.

The proposed Pharmacovigilance Plan also includes the activities performed for all licensed GSK vaccines, which enable safety signal detection as the post-marketing safety database continues to build. These activities include systematic and regular review of AEs that GSK receives from spontaneous reports, both on an individual and aggregated basis, and from other sources including the medical and scientific literature. Further elements GSK uses to support the planned pharmacovigilance activities include targeted follow-up questionnaires for AEs of interest, which help to improve the quality and consistency of safety data obtained from the reporter, as well as observed/expected analyses using published background rates to enhance signal detection.

9. FURTHER CLINICAL DEVELOPMENT

GSK is currently conducting a separate CDP in IC populations, including patients with stem cell transplant and renal transplant, and patients with solid malignant tumors and hematologic malignancies. GSK believes HZ/su has the potential to provide significant benefit to these patients. Most of these data were however not available at the time of the BLA submission (October 2016) and are therefore not discussed here. Once all data from this program are available, GSK will discuss the submission of these data with the FDA.

In addition, ongoing studies for the long-term follow-up of efficacy and immunogenicity, the concomitant administration of HZ/su with Tdap or pneumococcal vaccines, the administration of additional doses of HZ/su, as well as the assessment of HZ/su administered to subjects who previously received *Zostavax,* will be shared with regulatory authorities once available.

10. OVERALL DISCUSSION AND BENEFIT/RISK ASSESSMENT

10.1. Therapeutic Context

The majority of adults in the US is seropositive for VZV due to past VZV infection and therefore at risk for developing HZ and its complications, including PHN. Approximately 1 out of 3 US adults develops HZ over the course of their lifetime [CDC, 2008]. With increasing age, VZV-specific immunity wanes and the risk for PHN increases [Cohen, 2013].

Management of HZ is often suboptimal, particularly the treatment of the acute and chronic pain associated with HZ and PHN. The only licensed vaccine for the prevention of HZ is *Zostavax*, a live-attenuated vaccine. As demonstrated in phase III studies, *Zostavax* has a demonstrated VE of 70% in those 50-59 YOA, 51% in those ≥60 YOA, 41% in those 70-79 YOA, and 18% in those ≥80 YOA [*Zostavax* Prescribing Information, 2017]. While *Zostavax* offers the opportunity for prevention of HZ, its efficacy is not consistent across all age ranges, and effectiveness wanes to non-significant levels 8 to 11 years after vaccination [Schmader, 2012b; Morrison, 2015; Tseng, 2016; Baxter, 2017]. Prevention of HZ by a non-live vaccine that would offer high and long-term protection that is consistent across all age groups could further help to limit the burden of illness (BoI) caused by HZ and its complications. Therefore, the HZ/su vaccine has been developed to address this significant remaining unmet medical need in the prevention of HZ.

The gE antigen of VZV was selected as the vaccine antigen for HZ/su based on knowledge of its systems biology (its essential role in VZV replication and cell-to-cell spread) [Rahaus, 2003; Zerboni, 2014]. The AS01 adjuvant was selected to improve both the cellular and humoral immunity in the population of adults ≥50 YOA as was suggested by the pre-clinical and early clinical data. This improvement was important as data with the licensed HZ vaccine and other vaccines for this population indicated that achieving efficacy >70% would likely be a challenge, as the immune system ages and becomes less responsive.

10.2. Efficacy

Early phase clinical studies validated the assumptions used to select an adjuvanted sub-unit vaccine design for HZ/su. The dose of antigen and adjuvant in the final HZ/su formulation and the number of HZ/su doses and administration schedule are supported by robust clinical (and non-clinical) immunogenicity data. HZ/su is to be given by intramuscular route according to a two-dose schedule, with the flexibility of giving the second dose any time between 2 and 6 months after the first dose is administered.

In the pivotal Phase III efficacy studies (ZOSTER-006 and ZOSTER-022), high VE against HZ of 97.2% and 91.3% was demonstrated in adults ≥50 YOA (ZOSTER-006 final analysis) and in adults ≥70 YOA (ZOSTER-006/ZOSTER-022 pooled analysis), respectively, including adults in the oldest age group (≥80 YOA) with VE of 91.4%. The data show that VE estimates are consistent across all age strata. In adults ≥50 YOA, the HZ incidence was reduced from 9.1 per 1,000 person-years in the Placebo group to 0.3 per 1,000 person-years in the HZ/su group, and in adults ≥70 YOA, the HZ incidence was reduced from 9.3 per 1,000 person-years in the Placebo group to 0.8 per 1,000 person-years in the HZ/su group. VE against HZ remained high during yearly follow-up periods up to 4 years in adults ≥50 YOA and ≥70 YOA (i.e., 93.1% and 87.9% during the fourth year, respectively).

VE against PHN of 100% and 88.8% was demonstrated in adults ≥50 YOA (ZOSTER-006) and adults ≥70 YOA (ZOSTER-006/ZOSTER-022 pooled analysis). In addition, these studies also provided evidence of prevention of other HZ-associated complications. Overall, there was a trend towards less severe HZ-associated pain in subjects vaccinated with HZ/su compared to Placebo.

ZOSTER-006 and ZOSTER-022 were conducted in 18 countries distributed over different regions of the world (North America, Australia/Asia, Europe, Latin America), and included a broad population with limited exclusion criteria, to allow inclusion of subjects with a wide range of pre-existing medical conditions, provided the subject was medically stable enough for clinical trial participation, and the subject was not taking immunosuppresive medication. There did not appear to be meaningful regional differences in terms of HZ and PHN prevention as concluded from the region-specific sensitivity analysis performed in these global efficacy studies, implying that the overall efficacy data can be extrapolated to different regions.

The vaccine-induced antigen-specific immune responses in adults ≥50 YOA were consistently high 1 month post Dose 2 in all age strata. Although the antigen-specific immunogenicity decreased shortly after vaccination, persistence data out to approximately 6 years after the second dose showed that gE-specific CMI and humoral immune responses remained, respectively, 3.8-fold and 7.3-fold above the pre-vaccination levels in subjects who were ≥60 YOA at the time of vaccination.

Taken together, these data indicate that, if licensed, HZ/su could result in highly effective prevention of HZ in adults ≥50 YOA. And by preventing HZ, HZ/su would also prevent associated complications, such as PHN.

10.3. Safety Summary

The overall safety profile of HZ/su is found to be acceptable; no safety concerns have been identified based on thorough analysis of HZ/su safety data from the main safety pooling and the individual Phase II and Phase III HZ/su studies available from the CDP in the target population of adults ≥50 YOA.

The main safety pooling analysis was performed on a large dataset of the CDP (>85% of subjects ≥50 YOA who received HZ/su in the overall safety analysis) and documented the safety of HZ/su in adults ≥50 YOA from different regions and of different ethnicities.

Solicited local and general symptoms reported within 7 days post vaccination were more frequent in the HZ/su group than in the Placebo group, which is consistent with a short-term, localized inflammatory response induced by HZ/su. This is consistently observed in studies evaluating AS01 and other adjuvanted vaccines, in which higher rates of mostly mild to moderate and self-limited local and systemic reactions are observed with adjuvanted versus non-adjuvanted vaccines [Stassijns, 2016]. Results were aligned with data generated in Phase II studies (e.g., ZOSTER-010 and ZOSTER-003). The most common AEs observed in the 7 days after vaccination included local symptoms at the injection site (pain, redness and swelling) and general symptoms (myalgia, fatigue and headache). The majority of these solicited symptoms were mild to moderate in severity, and self-limited with a median duration of at most 3 days.

The compliance with the second vaccine dose was >95% in the main safety pooling. The drop-out rate due to (S)AEs was low in both HZ/su and Placebo groups.

The incidence of unsolicited AEs was comparable between the groups for the Day 7 through Day 29 follow-up period. The majority of the imbalances in terms of unsolicited AEs between HZ/su and Placebo recipients are mainly due to the rates of non-serious reactions which occurred in the first 7 days following vaccination such as injection site reactions and other local and general symptoms that are commonly associated with vaccination.

The available data showed that the incidence of SAEs was similar in HZ/su and Placebo recipients across both age strata and during all follow-up time periods analyzed, with a frequency of ~10% for all SAEs and ~0.1% for related SAEs (as per investigator assessment) in each group up to 365 days post last vaccination. Overall, there were no relevant imbalances observed in any of the groups. The most frequently reported SAEs when classified by SOC were cardiac disorders, followed by infections and infestations (mainly of the respiratory tract) and neoplasms (benign, malignant and unspecified). The majority of SAEs appeared to be associated with known risk factors in the target/studied population (e.g., advanced age). Based on the review of available safety data on major adverse cardiovascular and cerebrovascular events selected for further analyses, no safety concerns have been identified.

Fatal SAEs were also balanced between the HZ/su and Placebo group. The majority of fatal cases occurred in the older age group (≥70 YOA), with time to onset longer than one year after vaccination. Events with fatal outcome were notably cardiovascular (including

cardiac failure, cardiac arrest and myocardial infarction), pneumonia and lung cancer, which is aligned with the most frequent known causes of death in the overall population in the US [AARP, 2009] and Europe [RIVM, 2012]. There was one fatal SAE reported d with causal association to HZ/su (as per investigators assessment) in ZOSTER-022 (i.e., neutropenic sepsis in a patient who developed AML after long-standing thrombocytopenia). GSK considers the causal association with the vaccine as unlikely based on the nature of the event (no biological plausibility).

The data from the main safety pooling analysis showed that pIMDs were equally distributed between the HZ/su and Placebo group during all follow-up time periods analyzed, with a frequency of ~1% for all pIMDs and 0.1% for related pIMDs (as per investigator assessment) in each group during the entire post-vaccination follow-up period. No cluster was observed in terms of events reported or time-to-onset. The incidence of pIMDs was balanced between age groups and approximately half of the pIMDs occurred with time to onset longer than one year after last vaccination. The most frequent pIMD events reported by PT in the HZ/su and Placebo groups were polymyalgia rheumatica, rheumatoid arthritis and psoriasis. These events are also frequently observed in the general population of adults ≥50 YOA.

Following an assessment of risks of inflammation after exposure to HZ/su, a numerical imbalance in the reporting rate of gout (including gouty arthritis) as unsolicited AE was identified for which a biologically plausible relationship with vaccination cannot be excluded at this point. GSK considers the event of gout to be an AE of interest and plans to include it in the active safety surveillance activities of the proposed Pharmacovigilance Plan.

No case of HZ/su-related anaphylaxis has been reported in any study included in the BLA. The incidence of major adverse cardiovascular and cerebrovascular events (fatal and non-fatal) was similar in the HZ/su and Placebo groups.

During the entire study period, 9 HZ breakthrough cases in ZOSTER-006 and 23 HZ breakthrough cases in ZOSTER-022 were reported. Five of the breakthrough cases in ZOSTER-022 were associated with HZ-related complications, including 4 cases of PHN and one case with an ophthalmic complication (blurred vision). HZ breakthrough cases reported in ZOSTER-006 and ZOSTER-022 did not show any specific common pattern such as clinical presentation or underlying medical conditions.

The reactogenicity and safety profile of HZ/su in North American subjects from the main safety pooling were comparable with that in the overall population; no safety concern was identified.

The safety results from all other individual studies in adults ≥50 YOA included in the BLA were overall consistent with those from the main safety pooling, and revealed no safety concerns.

HZ/su has an overall clinically acceptable safety profile when co-administered with a seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine (ZOSTER-004). HZ/su has also shown a clinically acceptable safety profile when administered to a limited number of adults (including 96 subjects ≥50 YOA) with history of HZ

(ZOSTER-033). However additional studies are warranted in this population to confirm the safety profile in this population. In addition, HZ/su has an overall clinically acceptable safety profile when administered to IC adults ≥18 YOA (subjects with autologous hematopoietic stem cell transplant in ZOSTER-001 and subjects with HIV infection in ZOSTER-015).

In conclusion, the safety profile of HZ/su has been well characterized and found to be acceptable. Solicited local and general symptoms, reported within 7 days post vaccination were more frequent in the HZ/su group than in the Placebo group, which is aligned with the understanding of the mode of action of the vaccine. However, the majority of these symptoms were mild to moderate in severity, and self-limited with a median duration of at most 3 days, and no significant impact on compliance with Dose 2 was seen in the HZ/su group. The incidence of SAEs, fatalities and pIMDs was similar in the HZ/su and Placebo groups during all follow-up time periods analyzed, and the specific events reported were as expected for this age group.

10.4. Overall Benefit-risk Conclusions

The results of the pivotal Phase III efficacy studies (ZOSTER-006 in ≥50 YOA and ZOSTER-022 in ≥70 YOA) support the proposed indication: "*Prevention of HZ in adults ≥50 YOA. By preventing HZ, HZ/su also reduces the overall incidence of PHN*."

The consistent efficacy estimates against HZ, which were >91% regardless of age stratum, confirmed the success of the strategy to combine a single protein antigen (gE) and Adjuvant System ($AS01_B$) designed to enhance both CMI and humoral immunity. Therefore, HZ/su is expected to provide a substantial clinical benefit, and help to address the remaining unmet medical need in the target population of adults ≥50 YOA. The known mechanism of action of AS01, which induces a local and transient activation of the innate immune system, translates into higher reported rates of solicited symptoms compared to the saline placebo. However, the majority of these solicited symptoms were mild to moderate in severity and of self-limited duration, which again was in line with what was expected given the transient nature of the AS01 effect. The solicited symptoms did not appear to significantly deter subjects from receiving the second HZ/su dose, as compliance rates with the two-dose vaccination schedule were >95% in both treatment groups in the main safety pooling. Overall, the safety data from the main safety pooling and the individual Phase I-II and III HZ/su studies in the target population of adults ≥50 YOA do not raise safety concerns and support the acceptable safety profile of HZ/su.

In conclusion, vaccination of adults ≥50 YOA with HZ/su has been proven to be highly effective in preventing HZ and its debilitating complications, including PHN. The higher rates of solicited symptoms in HZ/su recipients were expected and consistent with the described mode of action of HZ/su, with the majority of symptoms being mild to moderate in severity and self-limited (median duration of ≤3 days). The benefit-risk profile of HZ/su will continue to be evaluated through a comprehensive Pharmacovigilance Plan to further monitor AEs after HZ/su vaccination. These AEs will include, but will not be limited to, a pre-defined list of AEs of interest, that will be agreed with regulatory authorities. The active safety surveillance, including a TSS, will enable

GSK to further enhance the passive surveillance that is continuously performed for all licensed vaccines.

Based on all efficacy, immunogenicity and the overall safety data, GSK considers that the benefit-risk profile of HZ/su is favorable for routine vaccination of adults ≥50 YOA to prevent HZ.

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12. APPENDICES

Appendix Table 1 Overview of completed clinical studies included in the BLA and presented in this briefing document

Study ID	Study country(ies)	Primary purpose of the study	Population (age) Vaccination schedule	Study groups	Number of subjects	
					ATP cohort for immuno	TVC
Pivotal studies						
ZOSTER-006	Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan Mexico, South Korea, Spain, Sweden, Taiwan, United Kingdom, US	Phase III, randomized, observer-blind, pivotal efficacy and safety study in older adults ≥50 YOA. Follow-up (FU) driven by case accrual was pre-specified as at least 30 months after Dose 2 (actual median safety follow-up time 4.4 years).	Adults (≥ 50 YOA) stratified: 50-59 YOA, 60-69 YOA, 70-79 YOA and ≥80 YOA in a 8:5:3:1 ratio 2 doses at Months 0 and 2	1) HZ/su 2) Placebo (saline)	1,070 (humoral immuno M3)[a] 212 (CMI immuno M3)[a] 1,067 (humoral immuno M3)[a] 218 (CMI immuno M3)[a]	7,695 (EOS)[b] 7,344 (mTVC)[c] 7,710 (EOS)[b] 7,415 (mTVC)[c]
ZOSTER-022	Australia, Brazil, Canada, Czech Republic, Estonia, Finland, France, Germany, Hong Kong, Italy, Japan Mexico, South Korea, Spain, Sweden, Taiwan, United Kingdom, US	Phase III, randomized, observer-blind, pivotal efficacy and safety study in older adults ≥70 YOA. FU driven by case accrual was at least 30 months after Dose 2 (actual median safety follow-up time 4.2 years).	Adults (≥ 70 YOA) stratified: 70-79 YOA and ≥80 YOA in a 3:1 ratio 2 doses at Months 0 and 2	**ZOSTER-022:** 1) HZ/su 2) Placebo (saline) **ZOSTER-006/-022 pooled data:** 1) HZ/su 2) Placebo (saline)	387 (humoral immuno M3)[a] 412 (humoral immuno M3)[a] 1,457 (humoral immuno M3)[a] 1,479 (humoral immuno M3)[a]	6,950[b] 6,541 (mTVC)[d] 6,950[b] 6,622 (mTVC)[d] 14,645[b] 13,881 (mTVC)[e] 14,660[b] 14,035 (mTVC)[e]

Study ID	Study country(ies)	Primary purpose of the study	Population (age) Vaccination schedule	Study groups	Number of subjects		
					ATP cohort for immuno		TVC
ZOSTER-004	Canada, Germany, US	Phase III, randomized, open-label study, co-administration of HZ/su with seasonal, quadrivalent, unadjuvanted, inactivated influenza vaccine (FLU-D-QIV). Duration of FU: 12 months post last vaccination	Adults (≥ 50 YOA) 1) Co-Ad group: 2 doses HZ/su: Month 0 and 2 & 1 dose FLU-D-QIV: Month 0 2) Control group: 1 dose FLU-D-QIV at Month 0, followed by 2 doses HZ/su at Months 2 and 4	1) Co-ad 2) Control	386 395		413 415[e]
ZOSTER-007[f]	Belgium, Canada, US	Phase III, randomized, double-blind, lot-to-lot consistency study. Duration of FU: 12 months post last vaccination	Adults (≥ 50 YOA) 2 doses HZ/su at Months 0 and 2.	1) HZ/su Lot A 2) HZ/su Lot B 3) HZ/su Lot C	210 210 202		218 217 216
ZOSTER-026	Estonia, US	Phase III, randomized, open-label, schedule comparison study. Duration of FU: 12 months post last vaccination	Adults (≥ 50 YOA) 1) Gr 0-2: 2 doses HZ/su at Months 0 and 2 2) Gr 0-6: 2 doses HZ/su at Months 0 and 6 3) Gr 0-12: 2 doses HZ/su at Months 0 and 12	1) Gr 0-2 2) Gr 0-6 3) Gr 0-12	**M3** 118 **M7** 114 **M13** 111	**M14** 117 **M18**[h] 115 **M24**[h] 110	119 119 116

Study ID	Study country(ies)	Primary purpose of the study	Population (age) Vaccination schedule	Study groups	Number of subjects					
					ATP cohort for immuno			TVC		
Supportive studies										
ZOSTER-003	Czech Republic, Germany, Netherlands, Sweden	Phase II, single-blind, randomized, antigen dose-selection study. Duration of FU: 1 month post last vaccination	Adults (≥ 60 YOA; Stratified: 60-69 YOA and ≥70 YOA in a 1:4 ratio) 2 doses at Months 0 and 2	1) gE251B: 25 μg gE/AS01$_B$	157			164		
				2) gE501B: HZ/su	156			166		
				3) gE1001B: 100 μg gE/AS01$_B$	151			165		
				4) gE100S: 100 μg gE/Saline	50			54		
				5) S gE1B: Saline, 1 dose, 100 μg gE/AS01$_B$, 1 dose	153			165		
ZOSTER-011, -012 and -013 (EXT 003 Y1, Y2, Y3)	Czech Republic, Germany, Netherlands Sweden	A single-blind extension follow-up at Months 12, 24 and 36 of ZOSTER-003 - persistence study. Duration of follow-up: 10, 22 and 34 months post last vaccination	ZOSTER-003 population No administration of HZ/su in this study		**M12**	**M24**	**M36**	**M12**	**M24**	**M36**
				1) gE251B: 25 μg gE/AS01$_B$	146	126	117	156	150	147
				2) gE501B: HZ/su	144	133	123	159	155	147
				3) gE1001B: 100 μg gE/AS01$_B$	147	135	127	159	154	150
				4) gE100S: 100 μg gE/Saline	48	44	40	50	49	47
				5) S gE1B: Saline, 1 dose, 100 μg gE/AS01$_B$, 1 dose	145	133	128	161	157	154
ZOSTER-024	Czech Republic, Germany, Netherlands Sweden	Phase II, open-label, single group, extension follow-up at Months 48, 60 and 72 of HZ/su group of ZOSTER-003 - persistence study. Duration of FU: 70 months post last vaccination	ZOSTER-003 population No administration of HZ/su in this study	1) gE501B: HZ/su	**M48** 126	**M60** NA	**M72** NA	**M48** 129	**M60** 124	**M72** 119
ZOSTER-010	Czech Republic, Spain, US	Phase II, randomized, observer-blind, adjuvant dose-selection study.	Adults (≥ 50 YOA)	1) gE/AS01$_B$: HZ/su	140			150		
				2) gE/AS01$_E$: 50 μg	138			149		

Study ID	Study country(ies)	Primary purpose of the study	Population (age) Vaccination schedule	Study groups	Number of subjects	
					ATP cohort for immuno	TVC
		Duration of FU: 12 months post last vaccination	2 doses at Months 0 and 2	gE/AS01$_E$, 3) gE/Saline: 50 μg gE/Saline 4) Saline	71 37	73 38
ZOSTER-033	Canada, Russian Federation	Phase III, non-randomized, open-label study in adults with a history of HZ. Duration of follow-up: 12 months post last vaccination.	Adults ≥50 YOA 2 doses HZ/su at Months 0 and 2	1) HZ/su	82	96

[a] TVC used for safety analysis
[b] mTVC used for final HZ efficacy analysis (Note: the mTVC for the EOS efficacy analysis included 7,340 subjects in the HZ/su group and 7,413 subjects in the Placebo group)
[c] mTVC used for efficacy analysis
[d] mTVC used for EOS efficacy analysis in the pooled dataset of ZOSTER-006 and ZOSTER-022
[e] Although 415 subjects were part of the TVC and received FLU-D-QIV at Dose 1, only 406 of them received at least 1 dose of HZ/su at the subsequent doses
[f] Only the active phase of ZOSTER-007 was completed (up to 1 month post last vaccination) at the time of submission.

Appendix Table 2 GSK list of Potential Immune-Mediated Diseases as of 30 June 2017

Neuroinflammatory disorders	Musculoskeletal disorders	Skin disorders
• Cranial nerve disorders, including paralyses/paresis (e.g. Bell's palsy) • Optic neuritis • Multiple sclerosis • Transverse myelitis • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Acute disseminated encephalomyelitis, including site specific variants: e.g. non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculoneuritis • Myasthenia gravis, including Lambert-Eaton myasthenic syndrome • Immune-mediated peripheral neuropathies and plexopathies, (including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy). • Narcolepsy	• Systemic lupus erythematosus and associated conditions • Systemic scleroderma (Systemic sclerosis), including diffuse systemic form and CREST syndrome Idiopathic inflammatory myopathies, including dermatomyositis • Polymyositis • Antisynthetase syndrome • Rheumatoid arthritis, and associated conditions including juvenile chronic arthritis and Still's disease • Polymyalgia rheumatica • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Psoriatic arthropathy • Relapsing polychondritis • Mixed connective tissue disorder • Gout	• Psoriasis • Vitiligo • Erythema nodosum • Autoimmune bullous skin diseases (including pemphigus, pemphigoid and dermatitis herpetiformis) • Alopecia areata • Lichen planus • Sweet's syndrome • Localised Scleroderma (Morphoea)
Vasculitides	**Blood disorders**	**Others**
• Large vessels vasculitis including: gianT-cell arteritis such as Takayasu's arteritis and temporal arteritis. • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome (allergic granulomatous angiitis), Buerger's disease (thromboangiitis obliterans), necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis.	• Autoimmune hemolytic anemia • Autoimmune thrombocytopenia • Antiphospholipid syndrome • Pernicious anemia • Autoimmune aplastic anaemia • Autoimmune neutropenia • Autoimmune pancytopenia	• Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Ocular autoimmune diseases (including autoimmune uveitis and autoimmune retinopathy) • Autoimmune myocarditis/cardiomyopathySarcoidosis • Stevens-Johnson syndrome • Sjögren's syndrome • Idiopathic pulmonary fibrosis • Goodpasture syndrome • Raynaud's phenomenon

Liver disorders	Gastrointestinal disorders	Endocrine disorders
• Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis • Autoimmune cholangitis	• Inflammatory Bowel disease, including Crohn's disease, ulcerative colitis, microscopic colitis, ulcerative proctitis • Celiac disease • Autoimmune pancreatitis	• Autoimmune thyroiditis (including Hashimoto thyroiditis) • Grave's or Basedow's disease • Diabetes mellitus type I • Addison's disease • Polyglandular autoimmune syndrome • Autoimmune hypophysitis

Appendix Table 3 HZ breakthrough cases in ZOSTER-006 and ZOSTER-022

Age *Country*	Gender	HZ start date	Duration of HZ episode (days)	PCR result	HZAC result	Complications
ZOSTER-006						
66 US	Male	1439 days post dose 2	99	Confirmed case	Not able to decide.	None
66 Canada	Male	460 days post dose 2	53	Confirmed case	No zoster.	None
50 Mexico	Female	535 days post dose 2	36	Confirmed case	Yes zoster	None
52 Finland	Female	1485 days post dose 2	45	Confirmed case	Yes zoster	None
56 Spain	Female	211 days post dose 2	24	Undetermined	Yes zoster	None
54 Taiwan	Male	484 days post dose 2	25	Confirmed case	Yes zoster	None
66 Japan	Female	1258 days post dose 2	85	Undetermined	Yes zoster	None
72 Japan	Male	521 days post dose 2	28	Confirmed case	Yes zoster	None
75 Finland	Female	1335 days post dose 2	36	Confirmed case	Yes zoster	None
ZOSTER-022						
80 Germany	Male	1345 days post dose 2	8	Confirmed	No zoster	None
70 Finland	Female	224 days post dose 2	~60	Undetermined	Yes zoster	None
86 Spain	Male	1307 days post dose 2	22	Confirmed	Yes zoster	None
78 Spain	Male	942 days post dose 2	33	Confirmed	Yes zoster	None
73 Spain	Male	1002 days post dose 2	24	Confirmed	Yes zoster	None
71 Czech Republic	Female	1317 days post dose 2	Unknown	Confirmed	Yes zoster	PHN confirmed. Itching and pain ongoing at study end (Jun 2015)
72 Czech Republic	Male	1319 days post dose 2	Unknown	Confirmed	Yes zoster	PHN confirmed. Pain ongoing at study end
86 Sweden	Female	390 days post dose 2	8	Confirmed	No zoster	None
78 Japan	Female	411 days post dose 2	28	Confirmed	No zoster	None
80 Taiwan	Male	716 days post dose 2	109	Confirmed	Yes zoster	PHN confirmed
73 Republic of Korea	Female	1124 days post dose 2	40	Confirmed	Yes zoster	None
71 Brazil	Female	682 days post dose 2	18	Undetermined	Yes zoster	None
80 Korea	Female	976 days post dose 2	166	Confirmed	Yes zoster	PHN confirmed

Age ***Country***	**Gender**	**HZ start date**	**Duration of HZ episode (days)**	**PCR result**	**HZAC result**	**Complications**
ZOSTER-006						
78 US	Female	1351 days post dose 2	63	No sample collected	Yes zoster	None
73 US	Female	1027 days post dose 2	96	Confirmed	Yes zoster	None
70 Mexico	Female	937 days post dose 2	25	Confirmed	Yes zoster	None
79 US	Female	928 days post dose 2	Unknown	Confirmed	Yes zoster	HZ related ophthalmic complication & headache
78 US	Female	477 days post dose 2	18	Confirmed	No zoster	None
73 US	Female	403 days post dose 2	37	Confirmed	Yes zoster	None
79 US	Male	1130 days post dose 2	36	Confirmed	Yes zoster	None
75 Germany	Male	1023 days post dose 2	37	Confirmed	Yes zoster	None
84 Germany	Female	526 days post dose 2	67	No sample taken	Yes zoster	None
72 Germany	Male	919 days post dose 2	38	Confirmed	Not able to decide	None