Systematic Review Report:
Efficacy and safety of adjuvanted herpes zoster subunit vaccine

Drug Assessment Working Group
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Abbreviations/Glossary

AE: adverse event
Anti-gE: anti-glycoprotein E
ARR: absolute risk reduction
AUC: area under the curve
CD4: Cluster of differentiation 4
CSR: Clinical Study Report
ELISA: Enzyme-linked Immunosorbent Assay
EQ-5D: Euro-Quality of Life - 5 Dimension
GSK: GlaxoSmithKline
HZ: herpes zoster
HZAC: Herpes Zoster Ascertainment Committee
IM: intramuscular
MID: minimal important difference
MPL: 3-O-desacyl- 4’-monophosphoryl lipid A
mTVC: modified total vaccinated cohort
NNV: number needed to vaccinate
PCR: polymerase chain reaction
PFU: Plaque-forming unit
pMID: potential immune-mediated disease.
QS21: Quillaja saponaria Molina, fraction 21
SAE: serious adverse event
SC: subcutaneous
SF-36: Short form health survey
TVC: total vaccinated cohort
VRR: vaccine response rate
VZV: varicella zoster virus
ZBPI: Zoster brief pain inventory
AS01ß: 1 mg dioleoyl phosphatidylcholine, 250 μg cholesterol, 50 μg MPL and 50 μg QS-21
AS01ε: 500 μg dioleoyl phosphatidylcholine, 125 μg cholesterol, 25 μg MPL and 25 μg QS-21
Executive Summary

1. Background
Herpes zoster (HZ) or “shingles” infection occurs through the reactivation of latent varicella zoster virus (VZV) in the sensory ganglia. The outbreak typically presents as a unilateral vesiculopustular rash along a dermatome, with accompanying pain. The rash and pain usually resolve over a few weeks. However, some patients develop persistent HZ-related pain referred to as post-herpetic neuralgia, or PHN. Estimates of the proportion of patients with HZ who develop PHN with some degree of pain lasting for at least 3 months range widely. The estimate most relevant to this review is that about 10% of non-immunized people who experience acute HZ still experience some pain at 3 months.

It is postulated that HZ occurs as a result of waning immunity. Vaccination has thus been developed to re-activate VZV cellular and humoral immune responses, and to help prevent a future HZ outbreak. Until early 2018, HZ vaccination was available only as a live attenuated vaccine. Disadvantages to the live vaccine are a reduced efficacy in adults older than 60-69 years, a waning protection over a few years regardless of age, and a contraindication for use in the immunosuppressed population.

Health Canada approved Shingrix, a non-living, recombinant, adjuvanted HZ subunit vaccine, for prevention of Herpes zoster (HZ). The vaccine is not approved by Health Canada for prevention of post-herpetic neuralgia (PHN).

2. Research Question
In immunocompetent adults aged ≥50, does vaccination with non-living, recombinant, adjuvanted HZ subunit vaccine differ from placebo, no vaccine or an alternative active vaccine in terms of a hierarchy of clinical safety and efficacy outcomes? Outcomes of interest include: all-cause mortality, SAEs, hospitalizations, quality of life, incidence of HZ, incidence of persistent HZ pain, severity of HZ pain, total physician visits, need for prescription medications, total withdrawals, withdrawals due to adverse events, and total adverse events.

3. Methods
A systematic literature search was conducted across CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS databases to identify relevant randomized controlled trials (RCTs). Data from eligible studies and their associated registry data and clinical study reports (CSRs) were extracted and analyzed by means of a meta-analysis whenever possible, or descriptively. Risk of bias was explored in all included studies and data interpreted according to this assessment. Our review findings were also compared to the conclusions of other independent review groups.
4. Results and Interpretations

Five RCTs met inclusion criteria, including 32,236 participants aged ≥50 years, of whom 15,009 subjects received at least one dose of adjuvanted HZ subunit vaccine. Three of the five RCTs compared HZ subunit vaccine to placebo and were meta-analyzed.

HZ incidence was significantly reduced in patients who received HZ subunit vaccine as compared with placebo (moderate quality evidence; 42 versus 520 HZ episodes over ~3.5 years; RR 0.07, 95% CI 0.03-0.22; I² = 90%; number needed to vaccinate = 31 over ~3.5 years). As a result of reduced HZ incidence, HZ-related complications such as persistent HZ pain (PHN) also decrease. Because only about 10% of older people experiencing shingles infection (HZ) progress to PHN, the absolute risk reduction in PHN is much smaller. The pooled PHN incidence in Shingrix vaccine trials was: Shingrix 0.06% vs placebo 0.34%; ARR =0.28%; number needed to vaccinate = 358 over ~3.5 years.

Analyses of subgroups based on age as well as time following vaccination were pre-specified in the protocols for the ZOE-50 and ZOE-70 trials (the largest efficacy trials to date). HZ incidence was reduced to relatively similar extents when comparing subgroups based on age, with ARRs in incidence at 2.97% for age 50-59, 4.1% for age 60-69, and 3.16% for age ≥70. The absolute risk reduction in HZ incidence rates by year following vaccination was comparable between each annual timeframe. Within year 1 post-vaccination, HZ incidence ARR was deemed to be 0.82%, and during year 4 post-vaccination the ARR was 0.81%

Solicited and freely reported AEs within the first seven days post-vaccination occurred at a significantly greater frequency than placebo (RR 2.24, 95% CI 2.16-2.33; I² = 0%; number needed to harm = 2 over ~3.5 years). Approximately 8 or 9 out of every 10 patients vaccinated experienced an AE, most commonly myalgias, fatigue or injection-site pain. The propensity for AEs did not appear to affect rates of study withdrawal, however, and reactions were typically classified as mild to moderate. Mortality or serious adverse events (SAEs) were not significantly increased with the HZ subunit vaccine versus placebo.

Leroux-Roels 2012 studied the safety and immunogenicity at twelve months post-vaccination with the HZ subunit vaccine versus the live attenuated Oka-strain VZV vaccine (two doses, two months apart), in a Phase I/II trial given as a single vaccine or concurrently. We report on the older (age 50-70) cohort of patients (n = 90) included in this study. Only reports of solicited AEs were available in the publication. Authors deemed the safety of the vaccines to be similar, noting that toxicities were generally mild to moderate in intensity and short-lived. Fatigue, fever, myalgia, headache and injection-site pain were more commonly reported by recipients of the HZ subunit vaccine than the Oka strain vaccine. No study withdrawals occurred on account of an AE.

For Leroux-Roels 2012 study results were not published on the trial registry entries on clinicaltrials.gov, and no CSR was available. Further outcome data was requested from study authors, who in turn forwarded the request to vaccine manufacturer GlaxoSmithKline (GSK). To date, no supplementary outcome data has been provided from GSK.

Chlibek 2014, a Phase II study involving 714 adults ≥60 years, studied the immunogenicity and safety of different formulations of HZ subunit vaccines (ranging from 25 to 100mcg of VZV gE,
with or without AS10\textsubscript{a} adjuvant) as well as different administration schedules for 36 months. Two doses, two months apart of a HZ subunit vaccine adjuvanted with AS01\textsubscript{b} was found to induce an acceptably strong and sustained immune response. Adverse events were more frequent in the adjuvanted vaccine arms. Injection site pain, myalgias and fatigue were the most common solicited adverse reactions.

5. Strengths of Review
RCT outcome data were available from over 15,000 subjects who received HZ subunit vaccine. Rigorous methods for assessing risk of bias and overall quality of evidence were used.

6. Limitations of Review
The populations studied had no history of HZ infection or previous HZ vaccination, and were immunocompetent, which may limit generalizability. Duration of protective effect for HZ subunit vaccine on incidence of HZ infection is still unclear. All included studies were manufacturer-funded. The efficacy of the vaccine is studied over a limited time period of 3.5 years and it is not known whether the protective effect will be maintained with time.

7. Other reviews of HZ subunit vaccine
The HZ subunit vaccine has been independently reviewed by Health Canada and NACI, the EMA, the FDA, and the CDC ACIP. These groups have each independently endorsed the efficacy of HZ subunit vaccine for HZ prevention in adults aged ≥50, with positive benefit to risk ratios. In addition to HZ prevention, the CDC and EMA recognize that the vaccine prevents PHN and other HZ-related complications.

The CDC supports a preferential use of HZ subunit vaccine over live vaccine in immunocompetent adults ≥50, based in part on cost-efficacy analyses.

8. Conclusions
- The two-dose HZ subunit vaccine series is effective in reducing HZ incidence, and therefore subsequent HZ-related complications (to a smaller absolute extent), in immunocompetent adults aged ≥50 years. Its use is associated with a high rate of adverse events, primarily local pain, myalgias and fatigue, which resolve within days. Its use does not increase the incidence of SAEs over placebo.
- The effectiveness (i.e. maintained protection) and safety of Shingrix are still unknown beyond about four years.
- Discuss the balance of baseline herpes zoster risk, harms, benefits and costs when considering this vaccine.
- Clinical outcome data is lacking in populations who have previously had HZ infection, or have previously received HZ vaccination.
1. Introduction
Over 90% of Canadian adults have a history of varicella zoster virus (VZV) infection, or "chickenpox." After acute VZV infection the virus establishes latency in the sensory ganglia, often for years or decades. It is postulated that a decrease in immunity, primarily cellular immunity, can prompt reactivation of the virus. The viral reactivation manifests as herpes zoster (HZ) or "shingles" infection.

Risk factors for HZ infection include increased age, immunosuppression, white race, female sex, stress, trauma, and diabetes. In the overall population, the lifetime risk for HZ is estimated to be thirty percent. In Canada this equates to about 130,000 annual cases per year, and 2000 hospitalizations. Recurrent cases happen in approximately six percent of patients.

The trend of HZ incidence appears to be increasing. Population-based data in British Columbia documented an increase in incidence from 3.2 per 1000 people in 1997 to 4.5 per 1000 in 2012. As a result of increasing HZ infection rates, the incidence of subsequent HZ-related complications can also be expected to rise.

HZ infection typically presents as a painful rash on a single side of the midline. It predictably follows the pattern of a dermatome, most frequently in the thoracic area or along the ophthalmic region of the trigeminal nerve. The rash may be preceded by prodromal pain or itching, after which erythematous macules or papules appear. These progress into vesicular lesions, then into pustules. The pustules typically crust over within the course of about ten days. In many patients, the HZ rash heals and painful symptoms resolve entirely within about four weeks. In up to about thirty percent of patients, however, the pain will persist for months beyond the initial rash, known as postherpetic neuralgia (PHN).

PHN is conventionally defined in the literature as pain persisting beyond either three or four months from the initial onset of rash. The pain may simply persist from the time of initial outbreak or it may be waning and recurrent in nature. PHN often requires prescription or non-prescription medications to alleviate symptoms and can have a considerable and long-term impact on quality of life and functioning. An older age at the time of HZ is associated with increased PHN-related pain and severity. Estimates of the likelihood that an older person with HZ will develop PHN vary widely. The most relevant and most recent estimate derives from clinical trials of the Shingrix vaccine (see below).

In 2008 the first vaccine for HZ prevention was marketed in Canada, the live vaccine Zostavax®. In a population of immunocompetent adults, use of the vaccine reduced the absolute incidence of HZ by 1.7% over approximately three years. With time the protective effect waned, to rates similar to placebo by five to six years from initial vaccination. PHN was reduced by an absolute rate of 0.27% during the same timeframe. Overall efficacy for HZ prevention appeared highest in the age range of 60 to 69 years and less when administered to older age groups. Because it is a live vaccine, its use is contraindicated in the immunosuppressed population.
As of early 2018, the first non-live HZ vaccine, known as Shingrix®, became commercially available in Canada (henceforth referred to as “HZ subunit vaccine”). It is supplied as a vial of lyophilized recombinant VZV surface glycoprotein E (gE) and an accompanying solution for reconstitution, which contains an adjuvant system AS01B [(Quillaja saponaria Molina fraction 21 (QS-21) and 3-O-desacyl-4′-monophosphoryl lipid A (MPL)]. When reconstituted, one dose (0.5mL) contains: VZV gE 50 mcg, QS-21 50 mcg and MPL 50 mcg. The dose must be administered intramuscularly.\textsuperscript{15}

In patients with past VZV exposure, the administration of the VZV gE (a major surface glycoprotein of VZV which on its own is unable to replicate) with an accompanying adjuvant induces an antigen-specific cell-mediated immunity as well as a humoral immune response thought to be protective against future viral dissemination. Administration of the adjuvant component induces an enhanced immune response via activation of molecular pathways of the innate immune system.\textsuperscript{15}

Shingrix is indicated by Health Canada for the prevention of HZ in adults aged 50 years and older. We aimed to systematically review the efficacy of the vaccine for the prevention of HZ and HZ-related persistent pain and sequelae, as well as its safety.

2. Research Question: PICOS format

Participants (P):
Immunocompetent adults aged ≥50

Intervention (I):
Non-live recombinant, adjuvanted HZ vaccine: VZV gE 50 mcg, QS-21 50 mcg and MPL 50 mcg (AS01B)

Comparators (C):
• Placebo
• No vaccination
• Active comparators (i.e., live attenuated vaccine)

Outcomes (O): Hierarchy as stated below:
1. All-cause mortality
2. Serious adverse events: FDA definition: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Also included are important medical events that may, based upon appropriate medical judgment, jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Number of patients with one SAE and also total number within study population.
3. All hospitalizations: Number of subjects with any hospitalization within study period.
4. Quality of life: As measured by scale in primary studies measuring functioning or QOL (i.e., Zoster Impact Questionnaire (ZIQ), SF-12 or -36, EuroQoL, etc) within the intervals:
   a. Each of: one, two, three, four, five, six or twelve months of initial onset of outbreak.
   b. Beyond twelve months.
5. **Incidence of herpes zoster (HZ):** Number of patients with one or more outbreaks, as well as total outbreaks. Clinical diagnosis as established by primary studies +/- PCR confirmation of VZV DNA in lesions.

6. **Incidence of HZ pain:** Number of subjects with pain associated with HZ outbreak site within:
   a. One month of initial onset of outbreak (“acute HZ pain”).
   b. Each of: two, three, four, five, six or twelve months of initial onset of outbreak.
   c. Beyond twelve months.
   Note that a conventional definition of “PHN,” using a somewhat arbitrary breakpoint of pain lasting for three or four months beyond the initial onset of rash was avoided here. We felt it more useful to capture pain that persisted at monthly intervals after an HZ outbreak, as this would better characterize the pain duration without excluding cases that did not meet the arbitrary cutoff.

7. **Severity of HZ pain:** Number of patients with mild, moderate or severe pain using validated pain scales. This outcome is partially captured in QoL as well. Worst (most severe) and mean pain associated with HZ. As measured by a validated pain scale in primary studies (i.e., Zoster Brief Pain Inventory Questionnaire (ZBPI), McGill Pain Questionnaire, etc), within:
   a. One month of initial onset of outbreak (“acute HZ pain”).
   b. Each of: two, three, four, five, six or twelve months of initial onset of outbreak.
   c. Beyond twelve months.

8. **Total physician visits:** Number of documented visits to medical doctor within study period.

9. **Need for prescription medications**

10. **Total withdrawals**

11. **Withdrawals due to adverse event**

12. **Total adverse events**

**Study Design (S):**
Randomized controlled trials (parallel group; open-label, double, triple or quadruple blind) with follow-up of at least 30 days post-vaccination will be included.

**3. Methods**

**Search strategy and findings**
The following databases were searched until June 2018: CENTRAL, MEDLINE, EMBASE, CINAHL, LILACS (search strategies outlined in Appendix 1). Relevant clinical study reports from the vaccine manufacturer (gsk-clinicalstudyregister.com), clinicaltrials.gov, WHO International Clinical Trials Registry Platform, Drugs@FDA, EMA were also sought out.

Independent reviews performed by groups such as Health Canada, the FDA, National Advisory Committee on Immunization (NACI), Advisory Committee on Immunization Practices (ACIP), EMA, NICE, AHRQ, Prescrire, and DTP were also sought out for summary and comparison if available.

Studies were selected for inclusion and perform data abstraction independently by two reviewers (EKR and IS). A third reviewer was involved in the case of discrepancy (VM).
Data collection and analysis
Data were collected from included studies in duplicate by two independent reviewers (ER and VM). Review Manager 5.3 software was used to meta-analyze applicable data. Results were pre-specified to be reported as relative risks (RR) with 95% confidence intervals for dichotomous outcomes and as weighted mean difference (WMD) with 95% confidence intervals for continuous outcomes.

Assessment of risk of bias in included studies
We assessed risk of bias according to Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions. We assessed seven domains: randomization and allocation concealment to assess selection bias; blinding of the participants and physician to assess performance bias; blinding of the outcome assessor to assess detection bias; incomplete outcome reporting to assess attrition bias; selective reporting of outcomes to assess selective reporting bias; and we added an additional category - other bias, to assess whether the study was funded by the manufacturer and conflict of interest was present, which we assessed as high risk of bias, since it has been shown to overestimate treatment effect.

Assessment of heterogeneity
Heterogeneity of treatment effect was tested between the trials using a standard Chi² statistic for heterogeneity. If significant between-study heterogeneity was identified, we used the random-effects model to test statistical significance. When heterogeneity was significant (I² greater than 50%), we attempted to identify trials that would contribute to the possible reasons of heterogeneity (explore their population characteristics, blinded or open-label study design, or response to placebo) that would possibly explain the reason for heterogeneity.

Publication bias
We had planned to use a funnel plot to assess the possibility of publication bias for outcomes that were reported in 10 or more studies. A test for funnel plot asymmetry (small study effects) formally examines whether the association between estimated intervention effects and a measure of study size is greater than might be expected to occur by chance.

Planned subgroup analyses
For efficacy outcomes including the incidence of HZ and HZ pain we chose to explore subgroups based on subject age, and time following vaccination (one year, two years, etc). We felt both of these variables were relevant to the interpretation and broader application of the outcome data. Analyses of both of the subgroups were pre-specified in the protocols for the ZOE-50 and ZOE-70 trials (the largest efficacy trials to date).

Assessment of overall quality of evidence
We considered five factors in grading the overall quality of evidence: limitations in study design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision in results, and high probability of publication bias. This approach specifies four levels of quality: high-, moderate-, low-, and very low-quality evidence. The highest quality rating is for randomized trial evidence. Quality rating is downgraded by one level for each factor, up to a maximum of three levels for all factors. If there are severe problems for any one factor (when assessing limitations in study design and implementation, in concealment of allocation,
loss of blinding, or attrition over 50% of participants during follow-up), randomized trial
evidence may fall by two levels due to that factor alone.

4. Results

Search results
Of 1031 citations, 5 RCTs met inclusion criteria (PRISMA flow diagram in Appendix 2). Clinical
study reports (CSRs), trial protocols or registry data supplemented these studies when
available. The 5 included trials enrolled a total of 32,236 participants aged ≥50 years, of whom
15,009 subjects received at least one dose of adjuvanted HZ subunit vaccine. Three studies
included a placebo arm as a comparator (Chlibek 2013, Lal 2015, Cunningham 2016), and
available outcome data from these studies were meta-analyzed. The remaining two studies
assessed safety against one or more active comparator. One involved a comparison to the live
attenuated Oka-strain VZV vaccine (Leroux-Roels 2012) and one comparing against alternative
Phase II candidate HZ subunit vaccine formulations prior to marketing (Chlibek 2014).

The two largest Phase III trials, analyzing over 29,000 participants collectively, are the ZOE-50
(Lal 2015) and ZOE-70 (Cunningham 2016) trials. These studies were conducted concurrently by
the same investigators at the same sites, and assessed the efficacy and safety of the adjuvanted
HZ subunit vaccine versus placebo injection in a population of adults ≥50 and ≥70 years
respectively. To date, these two trials are the only published reports which measure clinical
efficacy outcomes beyond immunogenicity, such as prevention of HZ and sequelae in
immunocompetent adults. Based on their scope and size, these studies will be the focus of this
report. The remaining studies provide us primarily with supplementary safety outcome data.

Risk of bias in included studies
Full risk of bias assessments for each identified study meeting the inclusion criteria are available
in Appendix 3.

Risk of bias graph: review authors' judgements about each risk of bias item presented as
percentages across all included studies.
Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

- **Random sequence generation**: was judged as low risk of bias in 3 studies [Chlibek 2013; Cunningham 2016 (ZOE-70) and Lal 2015 (ZOE-50)] and unclear risk of bias in 2 studies (Chlibek 2014 and Leroux-Roels 2012).

- **Allocation concealment**: was judged as low risk of bias in 3 studies [Chlibek 2013; Cunningham 2016 (ZOE-70) and Lal 2015 (ZOE-50)] and unclear risk of bias in 2 studies (Chlibek 2014 and Leroux-Roels 2012).

For the ZOE trials, three potential sources of bias were important to explore further: loss of blinding bias, incomplete outcome data, and selective reporting bias.

- **Blinding of participants and personnel**: was judged as low risk of bias in 2 studies [Cunningham 2016 (ZOE-70) and Lal 2015 (ZOE-50)] and high risk of bias in 3 studies (Chlibek 2013; Chlibek 2014 and Leroux-Roels 2012).
The ZOE trials were triple blinded (participant, investigator and outcome assessor). They were considered “observer blinded,” as the preparation and administration of study vaccines was by staff not involved in the study assessment (as visually, the active and placebo vaccines differed). Rates of adverse events, however, local and systemic, were much higher in the active HZ subunit vaccine arm than the placebo arm. These reactions could conceivably signal to investigators the treatment allocation of patients within the ZOE studies, if access to information about symptoms was available. Although blinding was not tested at end of the study, we judged it to be low risk of bias.

- **Blinding of outcome assessors:** was judged as low risk of bias in 3 studies [Chlibek 2013; Cunningham 2016 (ZOE -70) and Lal 2015 (ZOE-50)] and high risk of bias in 2 studies (Chlibek 2014 and Leroux-Roels 2012).

In the ZOE trials, a potential loss of blinding would become particularly relevant when considering the diagnosis of HZ cases in these trials. HZ diagnosis followed an algorithm that relied on the swabbing of outbreak lesions followed by PCR testing. If PCR testing was indeterminate, then a diagnosis was then made clinically, by a Herpes Zoster Ascertainment Committee (HZAC). The HZAC was 3-5 physicians who were also study investigators who had access to patient chart notes. Our concern was that patient chart notes describing reactions to the initial study vaccines could disrupt blinding and could influence the clinical diagnosis.

In ZOE-50, 366/478 (77%) of suspected HZ cases were confirmed by PCR as either positive or negative (72/96 in the HZ subunit vaccine arm and 294/382 in the placebo arm). In ZOE-70, 333/432 (77%) of suspected HZ cases were PCR-confirmed (58/87 in the HZ subunit arm and 275/345 in the placebo arm). The remaining approximately one-quarter of cases were therefore reliant on HZAC for diagnosis.

As a means for quality assurance, we computed “worst case” scenario calculations for these HZAC-confirmed cases. Using values obtained from the CSRs, we projected new proportions of HZ cases under the assumption that all suspected HZ cases in the HZ subunit group deemed negative by HZAC were in fact positive, and that all HZ cases deemed positive in the placebo arm by HZAC were in fact negative. With the “worst case” computation, a statistically significant reduction in HZ cases of relatively similar magnitude was still evident in both the ZOE-50 and ZOE-70 trials (see Appendix 5). Thus, we judged it as low risk of bias.

- **Incomplete outcome data:** was judged as low risk of bias in 2 studies (Chlibek 2013; Chlibek 2014) and as unclear risk of bias in 3 studies (Cunningham 2016 (ZOE -70) and Lal 2015 (ZOE-50) and Leroux-Roels 2012).

Collectively in ZOE-50 and ZOE-70, 30,977 subjects were enrolled. Of these, 1672 subjects were excluded from the TVC populations analyzed. Specifically, 37 subjects did not receive a study vaccine at all, and 1635 subjects were excluded due to study site closures or violations (819 in the HZ subunit arm, 815 in the placebo arm, and 1 subject not assigned to either arm). The majority of these excluded patients were attendees of a site closure in Mexico due to inappropriate oversight, unreliable documentation, and inadequate consent (671 from ZOE-50 and 865 from ZOE-70). These patients were
excluded entirely from any statistical analysis, and SAE information was reported separate from TVC analyses. No sensitivity analysis was reported for the closed site that we could find in the study CSRs.

Collectively the TVC of the ZOE-50 and ZOE-70 populations included 29,305 subjects. Of these, 4193 subjects withdrew over the course of the studies (2102 from the HZ subunit arms and 2091 from the placebo arms). These subjects were accounted for using a “last observation carried forward” strategy. The three primary reasons for withdrawal documented in CSRs were for consent withdrawal (“not due to an adverse event”) \( [n = 1505] \), SAE \( [n = 1405] \), and loss to follow-up \( [n = 522] \).

The rate of subject withdrawal is reported per study visit in the trial CSRs. Rates and patterns of withdrawal were similar between the HZ subunit and placebo arms in both trials (see summary Appendix 4). Though the relatively high withdrawal rate adds uncertainty to study results, to us, the balanced rate of withdrawal is reassuring in terms of assuming a similar impact of patient withdrawal in both treatment arms.

- **Selective reporting bias:** was judged as low risk for 1 study Chlibek 2013; high risk in 1 study Chlibek 2014 and unclear risk in 3 studies (Cunningham 2016 (ZOE-70) and Lal 2015 (ZOE-50) and Leroux-Roels 2012)

The population analyzed for efficacy outcomes and reported in the ZOE-50 and ZOE-70 publications was the “modified Total Vaccinated Cohort” (mTVC). This cohort excluded patients who did not receive their second study vaccine dose (due to withdrawal or having a HZ episode), or patients who had a HZ episode \( \leq 1 \) month after receiving their second study vaccine. The “total vaccinated cohort” (TVC), including every patient who received a study vaccine, was the population used for all safety analysis (most akin with intention-to-treat analysis).

A sensitivity analysis was performed using the TVC populations for efficacy outcomes, producing similar results. In our opinion, however, the TVC population is most appropriate to use for all analyses in randomized controlled trials of an intervention. We therefore specifically sought out TVC data for the analyses in our report, and present these unless otherwise stated. Discrepancies from mTVC values in the published manuscripts will be highlighted.

- **Other bias:** we considered funding of the study by the vaccine manufacturer. All 5 studies (Chlibek 2013; Chlibek 2014; Cunningham 2016 (ZOE-70) and Lal 2015 (ZOE-50) and Leroux-Roels 2012) were funded by GlaxoSmithKline.
Outcomes:

1. **HZ subunit vaccine versus placebo**

   **All-cause mortality**

   No difference in all-cause mortality was recognized in patients who received HZ subunit vaccine versus placebo (Chlibek 2013, ZOE-50 and ZOE-70) [RR 0.93, 95% CI 0.84-1.04; n = 29,499; Comparison 1].

   **Comparison 1: All-cause mortality**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HZ subunit vaccine</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio</th>
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<td></td>
<td>Events</td>
<td>Events</td>
<td>Total</td>
<td>M-H Fixed, 95% CI</td>
<td>M-H Fixed, 95% CI</td>
</tr>
<tr>
<td>Chlibek 2013</td>
<td>1</td>
<td>150</td>
<td>0</td>
<td>0.93 [0.84, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Cunningham 2016</td>
<td>426</td>
<td>6850</td>
<td>450</td>
<td>0.93 [0.82, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Lal 2015 (ZOE-60)</td>
<td>268</td>
<td>7698</td>
<td>221</td>
<td>0.94 [0.78, 1.14]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14798</strong></td>
<td><strong>14701</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.93 [0.84, 1.04]</strong></td>
<td></td>
</tr>
</tbody>
</table>

   No difference in the number of subjects with ≥1 SAE was found (Chlibek 2013, ZOE-50 and ZOE-70) [Subjects with ≥1 SAE RR 0.97, 95% CI 0.91-1.03; n = 29,499; Comparison 2].

   **Comparison 2: Subjects with ≥1 SAE during entire study period**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HZ subunit vaccine</th>
<th>Placebo</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Events</td>
<td>Total</td>
<td>M-H Fixed, 95% CI</td>
<td>M-H Fixed, 95% CI</td>
</tr>
<tr>
<td>Chlibek 2013</td>
<td>10</td>
<td>150</td>
<td>29</td>
<td>0.84 [0.74, 0.96]</td>
<td></td>
</tr>
<tr>
<td>Cunningham 2016</td>
<td>1153</td>
<td>6850</td>
<td>1214</td>
<td>0.96 [0.88, 1.04]</td>
<td></td>
</tr>
<tr>
<td>Lal 2015 (ZOE-60)</td>
<td>727</td>
<td>7698</td>
<td>731</td>
<td>1.00 [0.90, 1.10]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14798</strong></td>
<td><strong>14701</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.97 [0.91, 1.03]</strong></td>
<td></td>
</tr>
</tbody>
</table>

   However, the total numbers of SAEs were higher in ZOE 70 study (1908/6950 vs 2173/6950) as compared to ZOE 50 study (1136/7698 vs 1141/7713). This is explainable by the age difference between the ZOE populations, with the older adults in ZOE-70 being prone to higher rates of SAEs due to their more advanced age, and conceivably multiple SAEs at once. The mean follow-up in ZOE-70 was additionally longer than that of ZOE-50.
Hospitalizations
Total subjects with ≥1 hospitalization was available in the CSRs of ZOE-50 and ZOE-70, and were found to be similar in patients who received the HZ subunit vaccine versus placebo [RR 0.98, 95% CI 0.92-1.04; n = 29,311; Comparison 3].

**Comparison 3: Subjects with ≥1 Hospitalization**

<table>
<thead>
<tr>
<th>Study of Subgroup</th>
<th>ZOE-50</th>
<th>ZOE-70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>965</td>
<td>610</td>
</tr>
<tr>
<td>Placebo Events</td>
<td>965</td>
<td>610</td>
</tr>
<tr>
<td>Total Events</td>
<td>1930</td>
<td>1220</td>
</tr>
<tr>
<td>Total Weight</td>
<td>625%</td>
<td>37.5%</td>
</tr>
<tr>
<td>M.H. Fixed, 95% CI</td>
<td>0.97 [0.90, 1.04]</td>
<td>1.08 [0.90, 1.11]</td>
</tr>
<tr>
<td>Risk Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk of Bias</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Quality of Life (QOL)**
ZOE-50 and ZOE-70 measured QOL using the Short Form Health Survey (SF-36) and the Euro-Quality of Life - 5 Dimension (EQ-5D) scores weekly in patients with confirmed HZ. Results were presented for the mTVC population of subjects for whom questionnaires were available and evaluable (i.e., subjects who had first QOL evaluation visit within 14 days of the onset of rash). This represented a very small proportion of all randomized patients:

- **ZOE-50**: 9/7698 (0.1% of TVC) in HZ subunit arm, 252/7713 (3.3% of TVC) in placebo arm
- **ZOE-70**: 23/6950 (0.3% of TVC) in HZ subunit arm, 221/6950 (3.2% of TVC) in placebo arm

Zoster brief pain inventory (ZBPI) score was also considered as a QOL component (mean ZBPI worst pain score, mean ZBPI average pain score, mean activities of daily living (ADL) score). The ZBPI scores were similarly only assessed in patients with confirmed HZ in an evaluable mTVC population. This, too, is a very small proportion of originally randomized patients:

- **ZOE-50**: 8/7698 (0.1% of TVC) in HZ subunit arm, 241/7713 (3.1% of TVC) in placebo arm
- **ZOE-70**: 21/6950 (0.3% of TVC) in the HZ subunit arm, 208/6950 (3.0% of TVC) in the placebo arm

We feel it is inappropriate to draw firm conclusions from these comparisons. They represent an exceptionally small subgroup of patients initially randomized in the study, particularly in the HZ subunit vaccine arms.

For the information of the reader, however, findings are summarized below.

Amongst the scaled sub-categories of the SF-36 questionnaire in the ZOE-50 population, two of eight categories showed statistically significantly higher “worst scores” for the HZ subunit vaccine recipients over time. The p-values were not adjusted for multiple comparisons.

The categories were “bodily pain” (mean score 55.33 ± 16.85 for HZ subunit vaccine and 39.97 ± 24.59, p = 0.0338), and “role physical” (mean score 69.44 ± 19.63 for HZ subunit vaccine and 49.55 ± 31.45 for placebo, p = 0.0449). Scores range from 0-100, with lower scores suggesting
less disability. In ZOE-70, no statistically significant difference was found between any of the SF-36 subcategories when considering HZ subunit vaccine versus placebo over time. SF-36 utility scores were not statistically different between groups in ZOE-50 nor ZOE-70.

No statistically significant difference between HZ subunit vaccine and placebo was found overall with the worst mean EQ-5D scores in ZOE-50. In ZOE-70, the worst mean EQ-5D score for the mobility component was statistically significantly different, in favour of the placebo arm (28% of HZ subunit recipients versus 43% of placebo recipients reporting “no problems walking about” [p = 0.0468]). The mean worst EQ-5D utility score for the HZ subunit arm was 0.6874 ± 0.2651 versus 0.5329 ± 0.3615 for placebo (p = 0.1703). In ZOE-70, the mean worst EQ-5D utility score was 0.4918 ± 0.3978 for the HZ subunit group and 0.4809 ± 0.3626 for placebo (p = 0.6185). For EQ-5D, a minimal important difference (MID) is defined as a change of ~0.07 to ~0.08.

In ZOE-50, the mean “ZBPI average pain” score was statistically significantly less in the HZ subunit vaccine arm over time (3.9 ± 1.89 versus 5.5 ± 2.74 in placebo, p = 0.0486). No difference in “ZBPI worst pain” scores nor “ZBPI ADL” scores were evident. In ZOE-70, the “ZBPI worst pain” score was less in the HZ subunit vaccine arm over time (5.8 ± 3.06 versus 6.9 ± 3.05 in placebo, p = 0.0847). No statistical difference was found for “ZBPI average pain” score nor “ZBPI ADL” score over time. ZBPI uses a score of 0-10, with 10 indicating the highest level of pain.

Incidence of HZ

Chlibek 2013, ZOE-50 and ZOE-70 measured incidence of HZ in patients who received HZ subunit vaccine versus placebo. No HZ events occurred in the 14 months of follow up in Chlibek 2013. The incidence of HZ was significantly reduced in ZOE-50 and ZOE-70, with absolute rates of HZ of 0.28% in patients who received HZ subunit vaccine versus 3.54% in placebo over approximately 3.5 years [Subjects with ≥1 episode HZ RR 0.07, 95% 0.03-0.22; n = 29,493; TVC; Comparison 4]. Though the analysis is highly heterogeneous, this translates to an absolute risk reduction of 3.26% and a NNV of 31. We speculate that some of the heterogeneity could be explained by differences in patient withdrawal rates between ZOE-50 (approximately 12%) and ZOE-70 (approximately 17%). As data from the last point of patient contact was carried forward for analysis, a greater loss of patients in ZOE-70 throughout follow-up may have contributed to a lessened overall magnitude of effect between HZ subunit vaccine and placebo (less time for events).

**Comparison 4: Incidence of HZ**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Event Distribution</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subunit vaccine</td>
<td>Total</td>
<td>Placebo</td>
<td>Total</td>
<td>Weight</td>
<td>N: H: Random: 95% CI</td>
<td>N: H: Random: 95% CI</td>
</tr>
<tr>
<td>Chlibek 2013</td>
<td>0/510</td>
<td>0/510</td>
<td>0/116</td>
<td>0/116</td>
<td>52.1%</td>
<td>0.13 [0.05, 0.25]</td>
<td>0.04 [0.02, 0.09]</td>
</tr>
<tr>
<td>Cunningham 2016</td>
<td>30/650</td>
<td>240/650</td>
<td>240/770</td>
<td>240/770</td>
<td>47.9%</td>
<td>0.06 [0.02, 0.20]</td>
<td>0.06 [0.03, 0.16]</td>
</tr>
<tr>
<td>Lal 2015 (ZOE-50)</td>
<td>12/769</td>
<td>200/770</td>
<td>200/770</td>
<td>200/770</td>
<td>47.9%</td>
<td>0.07 [0.03, 0.22]</td>
<td>0.07 [0.04, 0.19]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>42/520</td>
<td>1479/1400</td>
<td>1668/1400</td>
<td>1668/1400</td>
<td>100.0%</td>
<td>0.08 [0.04, 0.20]</td>
<td>0.08 [0.04, 0.20]</td>
</tr>
</tbody>
</table>

Risk of bias: overall

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias
The published manuscripts of ZOE-50 and ZOE-70 report the analyses of HZ incidence using the mTVC populations. We feel this analysis inappropriately excludes patients and events, overestimating the reduction in HZ events with the use of HZ subunit vaccine. Below are mTVC and slightly more conservative TVC results for comparison (Table 1):

Table 1: Incidence of HZ by treatment arm in mTVC and TVC populations

<table>
<thead>
<tr>
<th></th>
<th>Incidence HZ: ZOE-50</th>
<th>Incidence HZ: ZOE-70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ s/u</td>
<td>Placebo</td>
</tr>
<tr>
<td>mTVC</td>
<td>9/7340 (0.12%)</td>
<td>245/7413 (3.3%)</td>
</tr>
<tr>
<td></td>
<td>23/6541 (0.35%)</td>
<td>223/6622 (3.37%)</td>
</tr>
<tr>
<td>TVC</td>
<td>12/7698 (0.16%)</td>
<td>280/7710 (3.6%)</td>
</tr>
<tr>
<td></td>
<td>30/6950 (0.43%)</td>
<td>240/6950 (3.5%)</td>
</tr>
</tbody>
</table>

Subgroups of interest
Additionally, we concluded that HZ incidence was reduced to relatively similar extents when comparing subgroups based on age, with ARRs in incidence at 2.97% for age 50-59, 4.1% for age 60-69, and 3.16% for age ≥70 (Table 2, see Appendix 6).

Table 2: HZ Incidence by Age: Pooled data from ZOE-50 and ZOE-70

<table>
<thead>
<tr>
<th>Age</th>
<th>HZ/su</th>
<th>Placebo</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-59</td>
<td>0.11%</td>
<td>3.08%</td>
<td>2.97%</td>
</tr>
<tr>
<td>60-69</td>
<td>0.27%</td>
<td>4.37%</td>
<td>4.1%</td>
</tr>
<tr>
<td>≥70</td>
<td>0.37%</td>
<td>3.53%</td>
<td>3.16%</td>
</tr>
</tbody>
</table>

Data as retrieved from ZOE-50 and ZOE-70 CSRs

We compared HZ incidence rates by year following vaccination, ARRs were comparable between each annual timeframe. Within year 1 post-vaccination, HZ incidence ARR was deemed to be 0.82%, and during year 4 post-vaccination the ARR was 0.81% (Table 3, see Appendix 6).

Table 3: HZ Incidence by Year: Pooled data from ZOE-50 and ZOE-70

<table>
<thead>
<tr>
<th>Year</th>
<th>HZ/su</th>
<th>Placebo</th>
<th>ARR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>0.05%</td>
<td>0.87%</td>
<td>0.82%</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.06%</td>
<td>1.18%</td>
<td>1.12%</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.1%</td>
<td>0.97%</td>
<td>0.87%</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.09%</td>
<td>0.90%</td>
<td>0.81%</td>
</tr>
</tbody>
</table>

Data as retrieved from ZOE-50 and ZOE-70 CSRs
Incidence of HZ pain
By virtue of reduced HZ incidence, it is predictable that HZ-related pain (which occurs exclusively as a consequence of the HZ outbreak) will be reduced.

We intended to quantify the proportion of patients who had any ongoing HZ-related pain at monthly intervals beyond the onset of HZ rash. This information was unavailable in the published manuscripts and CSRs for both ZOE-50 and ZOE-70, and attempts to obtain the information from study authors was unsuccessful. Instead, the incidence of PHN exclusively was quantified. PHN was defined as pain on the ZBPI ≥3, persisting or appearing 90 days after the initial onset of HZ rash. The information on pain was gathered specifically from the subgroup of subjects in the trials who had a confirmed HZ case (as described under “Quality of Life”).

In both publications, PHN incidence was reported as a proportion of subject in the entire mTVC populations. It is important to remember that pain was not measured in the population at large, but rather only in those patients with confirmed HZ.

PHN incidence as reported in the ZOE-50 and ZOE-70 studies has been summarized below. We have included both the mTVC and TVC populations (Table 4).

Table 4: Incidence of PHN by treatment arm in mTVC and TVC populations

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Incidence PHN: ZOE-50</th>
<th>Incidence PHN: ZOE-70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ s/u</td>
<td>Placebo</td>
</tr>
<tr>
<td>mTVC</td>
<td>0/7340 (0%)</td>
<td>18/7413 (0.24%)</td>
</tr>
<tr>
<td>TVC</td>
<td>0/7695 (0%)</td>
<td>21/7710 (0.27%)</td>
</tr>
</tbody>
</table>

The clinical study report of ZOE-70\textsuperscript{20a} (page 3209) presents pooled analysis (TVC) of the incidence of PHN in adults > 50 years: Shingrix: 8/14645 (0.06%) vs placebo: 50/14660 (0.34%), ARR 0.28%, NNV = 358; Vaccine efficacy with 95% CI = 83.94% (65.86%, 93.43%) p < 0.0001. The Canadian product monograph reports that in people over 70 “Shingrix significantly decreased the incidence of PHN” (ARR 1.1%, NNV = 91).\textsuperscript{22}

Severity of HZ pain
Similarly to the HZ pain incidence outcome above, pain severity was not reported in the ZOE publications in a means conducive for analysis. Inferences using PHN data (as pain for this outcome was assessed to be ≥3 on the ZBPI scale) is useful.

Total physician visits
Total physician visits were not a pre-specified outcome of the studies, and were not reported in the publications, registry data nor CSRs.

Need for prescription medications
The use of prescription medications was not reported for the overall population. The number of pain medications used was reported in the CSRs for ZOE-50 and ZOE-70 in the subset of patients who had confirmed HZ. Because this comparison is in a small subset of originally randomized
subjects, we feel it is inappropriate to draw conclusions from the data (though no difference in number of medications used was apparent between patients who had received the HZ subunit vaccine versus placebo in the analyses reported).

**Total withdrawals**

No difference in study withdrawals was found in Chlibek 2013, ZOE-50 and ZOE-70 [RR 1.01, 95% CI 0.95-1.07; n = 29,499; Comparison 5]. Withdrawal rates were considerable at approximately 12% and 17% overall in ZOE-50 and ZOE-70 trials respectively, but balanced between HZ subunit and placebo arms.

**Comparison 5: Total withdrawals**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Subunit vaccine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk of Bias A</th>
<th>Risk of Bias B</th>
<th>Risk of Bias C</th>
<th>Risk of Bias D</th>
<th>Risk of Bias E</th>
<th>Risk of Bias F</th>
<th>Risk of Bias G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlibek 2013 (ZOE-70)</td>
<td>1180</td>
<td>6950</td>
<td>1189</td>
<td>6950</td>
<td>56.9%</td>
<td>0.99 [0.92, 1.07]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>La 2013 (ZOE-50)</td>
<td>922</td>
<td>7698</td>
<td>902</td>
<td>7713</td>
<td>43.1%</td>
<td>1.02 [0.94, 1.12]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14798</strong></td>
<td><strong>14701</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.01 [0.95, 1.07]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Withdrawals due to adverse event**

Withdrawals attributed to an adverse event did not differ between HZ subunit and placebo [RR 1.01, 95% CI 0.91-1.11; n = 29,499; Comparison 6].

**Comparison 6: Total withdrawals due to AE**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Subunit vaccine</th>
<th>Placebo</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Risk of Bias A</th>
<th>Risk of Bias B</th>
<th>Risk of Bias C</th>
<th>Risk of Bias D</th>
<th>Risk of Bias E</th>
<th>Risk of Bias F</th>
<th>Risk of Bias G</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlibek 2013</td>
<td>1</td>
<td>150</td>
<td>0</td>
<td>29</td>
<td>0.1%</td>
<td>0.77 [0.92, 1.66]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham 2016 (ZOE-70)</td>
<td>563</td>
<td>6950</td>
<td>602</td>
<td>6950</td>
<td>86.4%</td>
<td>1.00 [0.88, 1.13]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>La 2013 (ZOE-50)</td>
<td>257</td>
<td>7698</td>
<td>253</td>
<td>7713</td>
<td>33.5%</td>
<td>1.02 [0.86, 1.21]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14798</strong></td>
<td><strong>14701</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>1.01 [0.95, 1.11]</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Total adverse events**

Adverse events were significantly higher in patients who received HZ subunit vaccine than placebo. In both ZOE-50 and ZOE-70, AEs were both solicited and reported freely within the first seven days post-vaccination in a subset of patients. When data were pooled, the rate subjects with ≥1 solicited or unsolicited AEs of any severity were 83.9% in those who received the HZ subunit vaccine versus 37.4% in the placebo arm [RR 2.24, 95% CI 2.16-2.33; n = 9,946; Comparison 7].
Comparison 7: Total solicited or unsolicited AEs within first seven days post-vaccination

The rate of unsolicited AEs within the first 30 days of vaccination in all patients in ZOE-50 and ZOE-70 was 50.3% in the HZ subunit vaccine group versus 31.9% in the placebo group [RR 1.59, 95% CI 1.37-1.84; n = 29,499; Comparison 8]. High heterogeneity in the analysis may have been influenced by the characteristics of subjects included in the 7-day solicited AE screening versus not included in the ZOE studies. ZOE-50 included far more patients than ZOE-70 in this solicited subgroup (8921 versus 1025), and those subjects not included in a solicited assessment would report all experienced AEs as unsolicited. Therefore it is unsurprising that a higher overall rate of unsolicited adverse events were evident with ZOE-70.

Comparison 8: Unsolicited AEs within 30 days post-vaccination

2. HZ subunit vaccine versus live attenuated OKA-strain VZV vaccine

Leroux-Roels 2012 studied the safety and immunogenicity at twelve months of the HZ subunit vaccine versus the live attenuated Oka-strain VZV vaccine in a Phase I/II trial (two doses, two months apart), given as a single vaccine or concurrently. Older (age 50-70) and younger (age 18-30) adults were included. Our analysis included only the older cohort of patients randomized to the HZ subunit vaccine or the Oka-strain live vaccine on its own (n = 90).

Safety of the vaccines was assessed by collecting both solicited and unsolicited reports of adverse events. Only reports of solicited AEs were available in the publication. Authors deemed the safety of the vaccines to be similar, noting that toxicities were generally mild to moderate in intensity and short-lived. Fatigue, fever, myalgia, headache and injection-site pain were more commonly reported by recipients of the HZ subunit vaccine than the Oka strain vaccine. No study withdrawals occurred on account of an AE.
Study data are presented in Table 5. Study results were not published on the trial registry entries on clinicaltrials.gov, and no CSR was available. Further outcome data was requested from study authors, who in turn forwarded the request to vaccine manufacturer GlaxoSmithKline (GSK). To date, no supplementary outcome data has been provided from GSK.

Table 5. Leroux-Roels I et al, 2012

<table>
<thead>
<tr>
<th></th>
<th>HZ subunit n = 45</th>
<th>OKA n = 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality:</td>
<td>0/45 (0%)</td>
<td>0/45</td>
</tr>
<tr>
<td>SAEs total:*</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Total subjects with &lt;1 SAE:*</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Incidence HZ: total subjects with ≥1 episode</td>
<td>0/45 (0%)</td>
<td>0/45 (0%)</td>
</tr>
<tr>
<td>Withdrawals:</td>
<td>0/45 (0%)</td>
<td>0/45 (0%)</td>
</tr>
<tr>
<td>Withdrawal due to any AE:</td>
<td>0/45 (0%)</td>
<td>0/45 (0%)</td>
</tr>
<tr>
<td>Withdrawals due to SAE:</td>
<td>0/45 (0%)</td>
<td>0/45 (0%)</td>
</tr>
<tr>
<td>Total adverse events:**</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

* “No vaccine-related SAEs” reported in publication, but total quantity not reported.
** Solicited reactions quantified but total solicited and unsolicited reactions not quantified in publication.

Note that other outcomes of interest: hospitalizations, quality of life, incidence of HZ pain, severity of HZ pain, total physician visits, and need for prescription medications were not assessed in this study.

3. HZ subunit vaccine versus alternate early candidate vaccine formulations/regimens

In a Phase II study involving 714 adults ≥60 years in 2014, Chlibek 2014 et al assessed different formulations of HZ subunit vaccines (ranging from 25 to 100mcg of VZV gE, with or without AS10ₐ adjuvant) as well as different administration schedules for 36 months (Table 6).

Immunogenicity and safety were assessed.

Two doses, two months apart of a HZ subunit vaccine adjuvanted with AS01ₐ was found to induce an acceptably strong and sustained immune response. Adverse events were more frequent in the adjuvanted vaccine arms. Injection site pain, myalgias and fatigue were the most common solicited adverse reactions.
<table>
<thead>
<tr>
<th>All-cause mortality:</th>
<th>HZ subunit n = 166</th>
<th>25 mcg gE/AS01\textsubscript{a} n = 164</th>
<th>100mcg gE/AS01\textsubscript{a} n = 165</th>
<th>S + 100mcg gE/AS01\textsubscript{a} n = 165</th>
<th>100mcg gE/S n = 54</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 166</td>
<td>8/166 (4.8%)</td>
<td>4/164 (2.4%)</td>
<td>4/165 (2.4%)</td>
<td>5/165 (3.0%)</td>
<td>4/54 (7.4%)</td>
</tr>
<tr>
<td>SAEs total:</td>
<td>71/166 (42.8%)</td>
<td>74/164 (45.1%)</td>
<td>90/165 (54.5%)</td>
<td>79/165 (47.9%)</td>
<td>35/54 (64.8%)</td>
</tr>
<tr>
<td>Total subjects with ≤1 SAE:</td>
<td>47/166 (28.3%)</td>
<td>42/164 (25.6%)</td>
<td>50/165 (30.3%)</td>
<td>50/165 (30.3%)</td>
<td>16/54 (29.6%)</td>
</tr>
<tr>
<td>Incidence HZ: total subjects with ≥1 episode</td>
<td>0/166 (0%)</td>
<td>2/164 (1.2%)</td>
<td>0/165 (0%)</td>
<td>1/165 (0.6%)</td>
<td>1/54 (1.9%)</td>
</tr>
<tr>
<td>Withdrawals:*</td>
<td>2/166 (1.2%)</td>
<td>3/164 (1.8%)</td>
<td>4/165 (2.4%)</td>
<td>1/165 (0.6%)</td>
<td>3/54 (5.6%)</td>
</tr>
<tr>
<td>Withdrawal due to any AE:*</td>
<td>1/166 (0.6%)</td>
<td>0/164 (0%)</td>
<td>2/165 (1.2%)</td>
<td>0/165 (0%)</td>
<td>0/54 (0%)</td>
</tr>
<tr>
<td>Withdrawals due to SAE:*</td>
<td>0/166 (0%)</td>
<td>0/164 (0%)</td>
<td>1/165 (0.6%)</td>
<td>0/165 (0%)</td>
<td>0/54 (0%)</td>
</tr>
<tr>
<td>Total adverse events: subjects with ≥1 AE (solicited or unsolicited) in 7-days post vaccination</td>
<td>146/166 (88.0%)</td>
<td>137/164 (83.5%)</td>
<td>142/165 (86.0%)</td>
<td>128/165 (77.6%)</td>
<td>27/54 (50%)</td>
</tr>
<tr>
<td>Total adverse events: Subjects with unsolicited AEs up to 30 days post-vaccination</td>
<td>52/166 (31.3%)</td>
<td>55/164 (33.5%)</td>
<td>54/165 (32.7%)</td>
<td>21/165 (after saline) (12.7%)</td>
<td>16/54 (29.6%)</td>
</tr>
</tbody>
</table>

HZ subunit: AS01\textsubscript{a}-adjuvanted 50mcg gE (2 doses, 2 months apart)
25 mcg gE/AS01\textsubscript{a}: AS01\textsubscript{a}-adjuvanted 25mcg gE (2 doses, 2 months apart)
100mcg gE/AS01\textsubscript{a}: AS01\textsubscript{a}-adjuvanted 100mcg gE (2 doses, 2 months apart)
S + 100mcg gE/AS01\textsubscript{a}: One dose saline (month 0) followed by one dose AS01\textsubscript{a}-adjuvanted 100mcg gE
100mcg gE/S: Unadjuvanted 100mcg gE/saline (2 doses, 2 months apart)
*Up to month 12
Note that other outcomes of interest: hospitalizations, quality of life, incidence of HZ pain, severity of HZ pain, total physician visits, and need for prescription medications were not assessed in this study.
4. HZ subunit vaccine in other studies

Additional studies that assessed the safety of the HZ subunit vaccine in an RCT but did not meet our inclusion criteria were reviewed (StrezoVA 2017, Schwarz 2017, Vink 2017, Lal 2018, Marechal 2018, NCT02052596).23-28 Similar safety patterns were evident. Total SAEs for patients who received HZ subunit vaccine occurred between a rate of 3.3% (Vink 2017, open-label, 12 month follow-up post-vaccine series) up to 15.3% (Schwarz 2017, open-label, 12 month follow-up post-vaccine series, co-administration with influenza vaccine).

The overall proportion of AEs of any type (including solicited) reported in HZ subunit vaccine recipients was common, occurring in approximately 8-9 out of 10 vaccine recipients. Injection site pain was the most common local reaction, and myalgia, fatigue and headache appeared to be the most common systemic reaction. Withdrawals in these studies related to adverse events were uncommon, occurring at a maximal rate of 1.7% (Schwarz 2017, open-label, 12 month follow-up post-vaccine series, co-administration with influenza vaccine). Overall withdrawals occurred at a maximal rate of 4.8% (NCT02052596, open-label, 12 month follow-up post-vaccine series, and administration with Boostrix vaccine).

5. Overall grading of evidence

The overall quality of evidence for HZ incidence (primary outcome measure) in the 3 placebo-controlled studies was graded based on the limitations in study design and implementation, indirectness of evidence, unexplained heterogeneity or inconsistency of results, imprecision in results, and high probability of publication bias. Cunningham 2016 (ZOE-70) and Lal 2015 (ZOE-50) studies contributed the most weight to the HZ incidence effect size. The study design was of highest quality (RCT). However, we downgraded the evidence by 1 level to moderate quality evidence due to judgement of unclear risk of bias for incomplete outcome data reporting as well as selective outcome reporting and significant inconsistency of results in the two studies which was partially explained differences in patient withdrawal rates between ZOE-50 (approximately 12%) and ZOE-70 (approximately 17%). As data from the last point of patient contact was carried forward for analysis, a greater loss of patients in ZOE-70 throughout follow-up may have contributed to a lessened overall magnitude of effect between HZ subunit vaccine and placebo (less time for events).

6. Discussion

Summary of available evidence

The available evidence supports that HZ subunit vaccine decreases the incidence of HZ infection in older adults, reducing the absolute rate of outbreaks by over three percent when compared to placebo over approximately 3.5 years. Our analysis concluded that HZ incidence was reduced by comparable magnitude when comparing subgroups based on age (aged 50-59, 60-69 and ≥70). PHN incidence also appeared to be modestly reduced by about 0.3% over the same timeframe.

Adverse events, most commonly pain at the vaccine injection site, general fatigue and muscle aches, and headache can be expected in most vaccine recipients (8 or 9 out of 10 vaccinated patients). More severe events limiting functioning and preventing normal activities “grade 3” events occurred in approximately 2 out of every 10 patients who received the HZ subunit vaccine. In general, these AEs resolved within 1 to 3 days in clinical studies, and did not appear to impact withdrawal rates from clinical studies over placebo. Expectations for AEs following the vaccine should be clearly communicated to patients considering the vaccine. Timing of the
administration may be strategically planned to align with a period with a lighter workload, for example, a weekend.

As HZ infection affects approximately one-third of Canadians in their overall lifetime, the decision to administer the vaccine may rely on the individual patient preference in terms of vaccine cost, and perceived value in HZ prevention.

**Strengths, limitations and unresolved questions**
The available evidence includes information on over 15,000 patients who received HZ subunit vaccine 0.5mL IM at 0 and 2 months in an RCT. Included patients tended not to be particularly frail. All included studies were sponsored by vaccine manufacturer GlaxoSmithKline.

Maintenance of the effect in reducing rate of HZ long-term is still unclear. To date, published data follows vaccinated patients for up to four years post-vaccination (ZOE-70). In their analysis (mTVC), “vaccine efficacy” changes from 97.0% during year 1 post-vaccination to 85.1% during year 4 post-vaccination. Some waning of effect is therefore apparent, but the extent is unknown. Long-term persistence of patients in the ZOE-50 and ZOE-70 trials is ongoing, including the exploration of administration of additional booster doses of the vaccine.29

Of interest, another study comparing the live attenuated HZ vaccine to HZ subunit vaccine for immunogenicity outcomes is ongoing.30 To our knowledge this is the first RCT comparing the two vaccines head to head.

**Special populations**
Of note, our included studies were limited to patients who had no history of HZ infection in the past. Use of HZ subunit vaccine has been explored in this population in a non-randomized study, which evaluated immunogenicity and safety outcomes only.31 In this study, humoral responses elicited to the HZ subunit vaccine were robust and comparable to responses in patients without a known history of HZ.

Patients who have previously received vaccination against HZ were also excluded from studies included in this review. An open-label, non-randomized Phase III study (n = 430) assessed immunogenicity and safety of the administration of HZ subunit vaccine in patients aged ≥65 who had received a live attenuated HZ vaccine ≥5 years previously when matched against similar adults not previously vaccinated.32 This study found similarly robust humoral responses and rates of AEs in included patients regardless of previous vaccination status.

Patients with immunodeficiency or receiving immunosuppressing medications are also subjects of study at present. The HZ subunit vaccine has shown satisfactory immunogenicity and safety profiles in patients living with HIV,33 stem cell transplant recipients,34,35 and renal transplant recipients.36

Because the HZ subunit vaccine is a two-dose series, it is also important to consider vaccine effect and response in those patients who do not complete the series. This effect was assessed by considering subjects within ZOE-50 who developed HZ after receiving their first dose in the series compared to those who did not develop HZ within this timeframe (mTVC). Authors conclude a vaccine efficacy of 90.79% (95% CI: 62.07% - 98.96%; mean follow up approximately 76 days).37
7. Other reviews of HZ subunit vaccine
The HZ subunit vaccine has been independently reviewed by Health Canada and NACI, the EMA, the FDA, and the CDC ACIP. These groups have each independently endorsed the efficacy of HZ subunit vaccine for HZ prevention in adults aged ≥50, with positive benefit to risk ratios.

In addition to HZ prevention, the CDC and EMA additionally also suggest the vaccine indication extend to include use for prevention of PHN or HZ-related complications.

Notably, the CDC supports a preferential use of HZ subunit vaccine over live zoster vaccine in immunocompetent adults ≥50, based in part by projected cost-efficacy analyses.

National Advisory Committee on Immunization (NACI) makes the following recommendations for individual level decision-making. NACI recommends that:

1. **RZV** should be offered to individuals ≥50 years of age without contraindications. (Strong NACI Recommendation, Grade A evidence)

2. **RZV** should be offered to individuals ≥ 50 years of age without contraindications who have previously been vaccinated with LZV. (Strong NACI Recommendation, Grade A Evidence)
   a. Re-immunization with 2 doses of RZV may be considered at least one year after LZV (Discretionary NACI Recommendation, Grade I evidence)

3. **RZV** should be offered to individuals ≥ 50 years of age without contraindications who have had a previous episode of HZ. (Strong NACI Recommendation, Grade B Evidence)
   a. Immunization with 2 doses of RZV may be considered at least one year after the HZ episode (Discretionary NACI Recommendation, Grade I evidence)

4. **LZV** may be considered for immunocompetent individuals ≥50 years of age without contraindications when RZV vaccine is contraindicated, unavailable or inaccessible. (Discretionary NACI Recommendation, Grade A evidence).

5. **RZV (not LZV)** may be considered for immunocompromised adults ≥50 years of age based on a case-by-case assessment of the benefits vs risks. (Discretionary NACI Recommendation, Grade I evidence). NACI will monitor results from ongoing trials in those who are immunocompromised and will reassess recommendations as evidence becomes available.

Note: [Grade A evidence is good evidence to recommend; Grade B evidence is fair evidence to recommend; Grade 1 is evidence from randomized controlled trial(s).]

8. Conclusions
- The two-dose HZ subunit vaccine series is effective in reducing HZ incidence, and therefore subsequent HZ-related complications (to a smaller absolute extent), in immunocompetent adults aged ≥50 years. Its use is associated with a high rate of adverse events, primarily local pain, myalgias and fatigue, which resolve within days. Its use does not increase the incidence of SAEs over placebo.
- The effectiveness (i.e. maintained protection) and safety of Shingrix are still unknown beyond about four years.
- Discuss the balance of baseline herpes zoster risk, harms, benefits and costs when considering this vaccine.
- Clinical outcome data is lacking in populations who have previously had HZ infection, or have previously received HZ vaccination.
9. References


25. ClinicalTrials.gov. Study to Assess the Immunogenicity and Safety of GlaxoSmithKline (GSK) Biologicals' Herpes Zoster Subunit (HZ/su) Vaccine (GSK1437173A) When Co-administered With GSK Biologicals' Diphtheria, Tetanus and Pertussis Vaccine (Boostrix®) in Adults Aged 50 Years


29. ClinicalTrials.gov. A Long-term Follow-up Study (ZOE-LTFU) of Two Studies 110390 (ZOSTER-006) and 113077 (ZOSTER-022) to Assess the Efficacy, Safety, and Immunogenicity Persistence of GSK Biologicals' Herpes Zoster Subunit (HZ/su) Vaccine and Assessment of 1 or 2 Additional Doses in Two Subgroups of Older Adults. [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT02723773) (accessed August 9, 2018).


8. Appendices

Appendix 1: Search Strategies
Database: Ovid MEDLINE(R) <1946 to Present with Daily Update>, Ovid MEDLINE(R) Epub Ahead of Print <June 11, 2018>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <June 11, 2018>
Search Date: 12 June 2018

1 herpes zoster/pc (945)
2 herpes zoster vaccine/ (610)
3 hz-su.mp. (33)
4 (shingles and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (28)
5 (zoster and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (204)
6 (hz and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (45)
7 shingrix.mp. (12)
8 GSK1437173A.mp. (2)
9 or/1-8 (1304)
10 randomized controlled trial.pt. (463543)
11 controlled clinical trial.pt. (92478)
12 randomized.ab. (414968)
13 placebo.ab. (189979)
14 dt.fs. (2026769)
15 randomly.ab. (292437)
16 trial.ab. (431964)
17 groups.ab. (1806972)
18 or/10-17 (4228158)
19 animals/ not (humans/ and animals/) (4437393)
20 18 not 19 (3655415)
21 9 and 20 (431)
22 remove duplicates from 21 (425)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2018>
Search Date: 12 June 2018

1 herpes zoster/pc (57)
2 herpes zoster vaccine/ (42)
3 hz-su.mp. (25)
4 (shingles and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (1)
5 (zoster and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (50)
6 (hz and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (25)
7 shingrix.mp. (1)
Database: Embase <1974 to 2018 June 12>
Search Date: 12 June 2018

1 herpes zoster/pc (1987)
2 varicella zoster vaccine/ (2649)
3 hz-su.mp. (43)
4 (shingles and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (40)
5 (zoster and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (466)
6 (hz and ((adjuvant$ or inactiv$ or non-live or recombinant or subunit) adj2 (immuni$ or vaccin$))).mp. (72)
7 shingrix.mp. (19)
8 GSK1437173A.mp. (1)
9 or/1-8 (3713)
10 randomized controlled trial/ (506160)
11 crossover procedure/ (55800)
12 double-blind procedure/ (150701)
13 (randomi?ed or randomly).tw. (1059557)
14 (crossover$ or cross-over$).tw. (94448)
15 placebo.ab. (265772)
16 (doubl$ adj blind$).tw. (190259)
17 assign$.ab. (333661)
18 allocat$.ab. (125537)
19 or/10-18 (1561395)
20 (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.) (6350155)
21 19 not 20 (1363289)
22 9 and 21 (295)
23 remove duplicates from 22 (287)

Database: EBSCO Embase
Search Date: 13 June 2018

S26 S9 AND S25 139
S25 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 694,366
S24 AB allocat* 24,726
S23 AB assign* 56,573
S22 TX clinical N1 trial* 319,440
S21 mask* 13,141
S20 blind* 87,183
S19 placebo* 50,972
S18 randomi* OR randomly 247,657
PT Clinical trial  87,180
MH "Placebos"  10,967
MH "Control Group"  10,873
MH "Control (Research)+"  11,068
MH "Comparative Studies"  158,461
MH "Clinical Trials+"  246,856
MH "Random Sample+"
MH "Random Assignment"  49,457
S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8  833
TX GSK1437173A  0
TX shingrix  36
(hz and ((adjuvant* or inactiv* or non-live or recombinant or subunit) N2 (immuni* or vaccin*)))))  14
(zoster and ((adjuvant* or inactiv* or non-live or recombinant or subunit) N2 (immuni* or vaccin*)))))  51
(shingles and ((adjuvant* or inactiv* or non-live or recombinant or subunit) N2 (immuni* or vaccin*)))))  11
hz-su  10
(MH "Herpes Zoster Vaccine")  329
(MH "Herpes Zoster+/PC")  620

Database: ClinicalTrials.gov
Search Date: 13 June 2018
Condition or disease: Herpes Zoster
Search Terms: randomized
Study type: Interventional Studies (Clinical Trials)
Intervention/treatment: adjuvant* OR GSK1437173A OR inactive* OR non-live OR recombinant OR shingrix OR subunit

Database: WHO International Clinical Trials Registry Platform (ICTRP)
Search Date: 13 June 2018
Condition: herpes zoster
Intervention: adjuvant* OR GSK1437173A OR inactive* OR non-live OR recombinant OR shingrix OR subunit
Recruitment status: ALL

Database: LILACS
Search Date: 13 June 2018
(tw:((culebrilla OR herpes OR hz-su OR shingles OR varicela OR zoster))) AND (tw:((adjuvant OR adjuvant* OR gsk1437173a OR inactiv* OR nao-viva OR nao-vivo OR non-live OR no-viva OR no-vivo OR recombinant* OR shingrix OR subunidad* OR subunit OR vacina* OR vacuna*))) AND (instance:"regional") AND ( db:"LILACS") AND type_of_study:"clinical_trials"
Appendix 2: PRISMA Flow Diagram

Records identified through database searching (n = 1031)

Additional records identified through other sources (n = 0)

Records after duplicates removed (n = 743)

Records screened (n = 743)

Records excluded (n = 719)

Full-text articles assessed for eligibility (n = 24)

Studies included in qualitative synthesis (n = 5)

Studies included in quantitative synthesis (meta-analysis) (n = 3)

Full-text articles excluded, with reasons (n = 19)
- Did not compare to placebo, no comparator or active vaccine (n = 8)
- Single-arm study (n = 3)
- Subsequent report of included study (n = 1)
- Immunosuppressed population (n = 7)
### Appendix 3: Table of Included Studies and Risk of Bias Assessments

<table>
<thead>
<tr>
<th>Study: Chlibek 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
</tr>
</tbody>
</table>
| **Participants**    | n = 410 adults aged ≥50 years. Excluded if:  
|                     | - confirmed or suspected immunosuppressive or immunodeficient condition or were receiving chronic (>14 days) immunosuppressants or immune-modifying drugs within ≤3 months of enrollment  
|                     | - had history HZ or previously vaccinated against HZ/VZV  
|                     | - had an acute disease at the time of enrollment or had allergic disease or reactions likely to be exacerbated by any component of the vaccine  
|                     | - were administered immunoglobulins or blood products within the 3 months preceding the first injection of study vaccine or planned to receive them during the study period, or were using any investigational or nonregistered drug/vaccine ≤30 days preceding the first dose of study vaccine or any nonreplicating vaccines within 2 weeks of enrollment  
|                     | - were pregnant or were of child-bearing potential and not using birth control |
| **Interventions**   | Randomized 4:4:2:1  
|                     | 2 doses, 2 months apart (months 0,2) of:  
|                     | 1. 50 μg gE/AS01B, 0.5 mL IM (n = 150)  
|                     | 2. 50 μg gE/AS01E, 0.5 mL IM (n = 149)  
|                     | 3. 50 μg gE/saline, 0.5 mL IM (n = 73)  
|                     | 4. Saline placebo, 0.5 mL IM (n = 38) |
| **Outcomes**        | - Frequency of gE-specific CD4+ T-cells expressing at least 2 different immunological activation markers [one month after the second vaccination (Month 3)]  
|                     | - Frequency of VZV-Specific CD4+ T-cells expressing at Least 2 Different Immunological Activation Markers [One month after the second vaccination (Month 3)]  
|                     | - Anti-gE Antibody Concentrations [One month after the second vaccination (Month 3)]  
|                     | - Anti-VZV Antibody Concentrations [One month after the second vaccination (Month 3)]  
|                     | - Frequencies of gE-specific CD4+ T-cells Expressing at Least 2 Different Immunological Activation Markers [At Month 0 and at Month 2]  
|                     | - Frequency of VZV-specific CD4+ T-cells Expressing at Least 2 Different Immunological Activation Markers [At Month 0 and at Month 2]  
|                     | - Anti-gE Antibody Concentrations [At Month 0 and at Month 2]  
|                     | - Anti-VZV Antibody Concentrations [At Month 0 and at Month 2]  
|                     | - Number of Subjects With Any and Grade 3 Solicited Local Symptoms [During the 7-day post-vaccination period after each dose and across doses] |
- Number of Subjects With Any, Grade 3 and Related Solicited General Symptoms. [During the 7-day post-vaccination period after each dose and across doses]
- Number of Subjects With Any, Grade 3 and Related Unsolicited Adverse Events (AEs) [Within the 30-day (Days 0-29) post-vaccination period]
- Number of Subjects With Serious Adverse Events (SAEs) [From Month 0 up to Month 8]
- Number of Subjects With Serious Adverse Events (SAEs) [During the period after Month 8 up to the end of the study at Month 14]
- Number of Subjects With Any New Onset of Autoimmune Diseases (NOADs) [From Month 0 until Month 8]
- Number of Subjects With Any New Onset of Autoimmune Diseases (NOADs) [During the period after Month 8 up to the end of the study at Month 14]
- Number of Subjects With Suspected Cases of Herpes Zoster (HZ) [From Month 0 until Month 8].
- Number of Subjects With Suspected Cases of Herpes Zoster (HZ) [During the period after Month 8 up to the end of the study at Month 14]
- Number of Subjects With Haematological and Biochemical Parameters Unknown, Below, Within or Above the Normal Ranges [At Month 0]
- Number of Subjects With Haematological and Biochemical Parameters Unknown, Below, Within or Above the Normal Ranges [At Month 2]
- Number of Subjects With Haematological and Biochemical Parameters Unknown, Below, Within or Above the Normal Ranges [At Month 3]

### Notes

#### Risk of Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors/ Judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>&quot;The randomization was made using an algorithm that stratified by country, minimized for age, and included a block size of 11&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>&quot;After having checked that a subject was eligible, and after informed consent had been obtained, the person in charge of the vaccination accessed the randomization system on internet using the subject number and age.&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Vaccine recipients were blinded but the person administering was aware of treatment allocation: &quot;the person in charge of the vaccination accessed the randomization system on internet using the subject number and age&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>&quot;observers responsible for evaluations were blinded to which formulation was administered.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>The study flow and disposition of all patients is clear.</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>----------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>Outcomes specified in trial registry match reporting.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funded by GlaxoSmithKline.</td>
</tr>
</tbody>
</table>

### Study: Chlibek 2014

**Methods**

- Phase II, single-blind (participant), parallel-group, age-stratified, multi-centre RCT.
- 11 centres in the Czech Republic, Germany, the Netherlands and Sweden.
- Duration: 36 months after first vaccination.

**Participants**

- n = 714 healthy adults ≥ 60 years at the time of first vaccination.
- Excluded if:
  - history of HZ or previously vaccinated against HZ or VZV.
  - previously vaccinated with any vaccine containing MPL or QS21 components.
  - were allergic to any vaccination components.
  - had received any vaccine (excluding influenza) within 2 weeks before first vaccine dose.
  - had received an investigational/non-registered product within 30 days prior to first vaccine dose.
  - on chronic immunosuppressants or corticosteroids within 3 months before the first vaccine dose.
  - had received immunoglobulins/blood products within 3 months of first vaccine dose.
  - history of drug or alcohol abuse.

**Interventions**

- Randomized 1:3:3:3:
  - 2 doses, 2 months apart (months 0,2) of:
    1. 100 μg gE/saline, 0.5 mL IM (n = 54)
    2. 25 μg gE/AS01B, 0.5 mL IM (n = 164)
    3. 50 μg gE/AS01B, 0.5 mL IM (n = 166)
    4. 100 μg gE/AS01B, 0.5 mL IM (n = 165)
    or
    5. 1 dose of saline 0.5 mL IM (month 0) followed by 1 dose of 100 μg gE/AS01B, 0.5 mL IM at month 2 n = 165

**Outcomes**

- Cell mediated immune response (CMI) in terms of frequencies of CD4 T cells specific for VZV antigens [One month after the second vaccination (Month 3)]
- CMI in terms of frequencies of CD4/CD8 T cells specific for VZV antigens [At months 0, 2, 3, 12, 24 and 36]
- VZV-specific Ab concentrations [At months 0, 2, 3, 12, 24 and 36]
- Frequency of VZV-specific memory B-cells in a subset of subjects [At months 0 and 3]
- Occurrence, intensity and relationship to vaccination of solicited local and general AEs [During 7 days after each vaccination]
- Occurrence, intensity and relationship to vaccination of unsolicited AEs [During 30 days after each vaccination]
- Occurrence and relationship to vaccination of all SAEs. [During the whole study period (day 0 to month 36)]
- Occurrence of clinically diagnosed HZ episodes during the whole study period. [Day 0 to month 36]
- Haematological and biochemical parameters. [At months 0, 2 and 3]
- Biochemical parameters [1 week after each vaccination]

### Notes

715 patients enrolled but 714 vaccinated

### Risk of Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors/ Judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation</td>
<td>Unclear risk</td>
<td>&quot;Subjects were stratified by age (60–69 years and ≥70 years in a 1:4 ratio) and randomized&quot; - method for randomization not specified.</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Unclear risk</td>
<td>As above, no description of group allocation was located.</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>High risk</td>
<td>Participants blinded but investigators were not. No description of attempts to conceal/match appearance of vaccines.</td>
</tr>
<tr>
<td>Blinding of outcome assessment</td>
<td>High risk</td>
<td>Outcome assessors were not blinded to treatment allocation.</td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>Patient flow is clearly documented and completion rate in safety cohort was 98%.</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>High risk</td>
<td>Not all secondary outcomes reported in full (memory B-cells, incidence HZ). Results about AEs, SAEs and mortality are reported descriptively only.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funded by GlaxoSmithKline.</td>
</tr>
</tbody>
</table>

### Study: Cunningham 2016 (ZOE-70)

<table>
<thead>
<tr>
<th>Methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III, triple blind (participant, care provider, outcomes assessor), parallel-group, age-stratified, region-stratified, region-stratified, placebo-controlled, multi-centre RCT.</td>
</tr>
</tbody>
</table>
| Participants | n = 13,900 adults age ≥70 years  
|--------------|------------------------------------------------------------------------------------------------------------------|
| - history of HZ or previously vaccinated against HZ or VZV.  
| - confirmed or suspected immunosuppressive or immunodeficient condition, or chronic administration (>15 days) of immunosuppressants or immune-modifying drugs within 6 months prior to the first vaccine dose.  
| - history of allergic disease/reaction likely to be exacerbated by any component of the vaccine  
| - acute disease or illness at the time of enrollment  
| - any conditions that might interfere with evaluations required in the study  
| - received immunoglobulins or blood products within the 90 days preceding the first dose of study vaccine or planned to receive such products during the study period  
| - administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination [licensed non-replicating vaccines could be administered up to 8 days before each dose or at least 14 days after any dose of study vaccine]  
| - participation in another clinical study, at any time during the study period- use of any investigational or non-registered drug/vaccine other than the study vaccine within 30 days preceding the first dose of study vaccine  
| - pregnant or were of child-bearing potential and not using birth control  
| Interventions | 2 doses, 2 months apart (months 0,2) of:  
| 1. Recombinant subunit zoster vaccine 50 μg gE/AS01B, 0.5 mL IM (n = 6950)  
| 2. Placebo, 0.5 mL IM (n = 6950)  
| Outcomes | - Confirmed HZ cases (in mTVC)  
| - PHN cases (in mTVC)  
| - Duration of severe ‘worst’ HZ-associated pain (severe = ZBPI score ≥3)  
| - Incidence of overall and HZ-related mortality  
| - Incidence of HZ complications (in subjects with confirmed HZ)  
| - Incidence of overall and HZ-related hospitalizations  
| - Duration of pain medication administered for HZ (in subjects with confirmed HZ)  
| - Solicited local and general symptoms in a subset of subjects [Occurrence, intensity of each solicited local and general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset]  
| - Unsolicited adverse events (AEs) in a subset of patients [Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 - 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects]  
| - Serious Adverse Events (SAEs) [months 0 - 14]  
| - Occurrence of pre-defined AEs (NOADs)  

18 centres in Europe, North America, Latin America, and Asia-Australia. Duration: Mean follow-up 3.7 years
- Occurrence of medically attended visits (months 0-8)
- Acute HZ severity (in subjects in mTVC with confirmed HZ)
- Interference of HZ with QoL (in subjects in mTVC with confirmed HZ)
- HZ BOI (in subjects in mTVC with confirmed HZ)
- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38
- Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38

Notes
Also presented pooled analyses with Lal 2015 - presented separately.

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Authors/Judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>&quot;Participants who were 70 years of age or older were first randomly assigned to either ZOE-50 or ZOE-70 and then were randomly assigned in a 1:1 ratio to either the HZ/su group or the placebo group with the use of an online centralized randomization system.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Study protocol: &quot;After having checked the eligibility of the subject and obtaining the signed ICF, the site staff in charge of the vaccination will access SBIR&quot; (SBIR is a centralized randomization system)</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>&quot;The investigators, participants, and persons responsible for evaluating the study end points were unaware of whether HZ/su or placebo had been administered.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>&quot;the persons responsible for evaluating the study end points were unaware of whether HZ/su or placebo had been administered.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Approximately 17% of subjects enrolled withdrew from TVC. Data collected until date of withdrawal/last contact were used for analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Reporting of efficacy outcomes using the mTVC was made more comprehensive with complete TVC numbers for many (but not all) outcomes. Primary outcomes outlined in protocol are reported, most secondary outcomes as well.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funded by GlaxoSmithKline.</td>
</tr>
</tbody>
</table>

Study: Lal 2015 (ZOE-50)

Methods
Phase III, triple blind, parallel-group, age-stratified, region-stratified, placebo-controlled, multi-centre RCT. 18 centres in Europe, North America, Latin America, and Asia-Australia.
## Participants

<table>
<thead>
<tr>
<th>Duration: Mean follow-up 3.2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 15,411 adults age ≥50 years.</td>
</tr>
<tr>
<td>Excluded if:</td>
</tr>
<tr>
<td>- history of HZ or previously vaccinated against HZ or VZV.</td>
</tr>
<tr>
<td>- confirmed or suspected immunosuppressive or immunodeficient condition, or chronic administration (&gt;15 days) of immunosuppressants or immune-modifying drugs within 6 months prior to the first vaccine dose.</td>
</tr>
<tr>
<td>- history of allergic disease/reaction likely to be exacerbated by any component of the vaccine</td>
</tr>
<tr>
<td>- acute disease or illness at the time of enrollment</td>
</tr>
<tr>
<td>- any conditions that might interfere with evaluations required in the study</td>
</tr>
<tr>
<td>- received immunoglobulins or blood products within the 90 days preceding the first dose of study vaccine or planned to receive such products during the study period</td>
</tr>
<tr>
<td>- administration of any other immunizations within 30 days before the first or second study vaccination or scheduled within 30 days after study vaccination [licensed non-replicating vaccines could be administered up to 8 days before each dose or at least 14 days after any dose of study vaccine]</td>
</tr>
<tr>
<td>- participation in another clinical study, at any time during the study period- use of any investigational or non-registered drug/vaccine other than the study vaccine within 30 days preceding the first dose of study vaccine</td>
</tr>
<tr>
<td>- pregnant or were of child-bearing potential and not using birth control</td>
</tr>
</tbody>
</table>

## Interventions

<table>
<thead>
<tr>
<th>2 doses, 2 months apart (months 0,2) of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Recombinant subunit zoster vaccine 50 μg gE/AS01B, 0.5 mL IM (n = 7698)</td>
</tr>
<tr>
<td>2. Placebo, 0.5 mL IM (n = 7713)</td>
</tr>
</tbody>
</table>

## Outcomes

| Confirmed HZ cases (in mTVC) |
| PHN cases (in mTVC) |
| Duration of severe ‘worst’ HZ-associated pain (severe = ZBPI score ≥3) |
| Incidence of overall and HZ-related mortality |
| Incidence of HZ complications (in subjects with confirmed HZ) |
| Incidence of overall and HZ-related hospitalizations |
| Duration of pain medication administered for HZ (in subjects with confirmed HZ) |
| Solicited local and general symptoms in a subset of subjects [Occurrence, intensity of each solicited local and general symptom within 7 days (Days 0-6) after each vaccination, in subjects included in the 7-day diary card subset] |
| Unsolicited adverse events (AEs) in a subset of patients [Occurrence, intensity and relationship to vaccination of unsolicited AEs during 30 days (Days 0 - 29) after each vaccination, according to the Medical Dictionary for Regulatory Activities (MedDRA) classification in all subjects] |
| Serious Adverse Events (SAEs) [months 0 - 14] |
| Occurrence of pre-defined AEs (NOADs) |
| Occurrence of medically attended visits (months 0-8) |
- Acute HZ severity (in subjects in mTVC with confirmed HZ)
- Interference of HZ with QoL (in subjects in mTVC with confirmed HZ)
- HZ BOI (in subjects in mTVC with confirmed HZ)
- CMI in terms of frequencies of antigen-specific CD4 T cells at Months 0, 3, 14, 26 and 38
- Antigen-specific Ab concentrations at Months 0, 3, 14, 26 and 38
- Anti-VZV neutralizing Ab titres at Months 0, 3, 14, 26 and 38

### Notes

#### Risk of Bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors/ Judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>&quot;We randomly assigned participants in a 1:1 ratio to receive either vaccine or placebo using an online centralized randomization system&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>Study protocol: &quot;After having checked the eligibility of the subject and obtaining the signed ICF, the site staff in charge of the vaccination will access SBIR&quot;</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>&quot;Because the appearance of the reconstituted HZ/su vaccine differed from the placebo solution, injections were prepared and administered by study staff who did not participate in any study assessment.&quot;</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>&quot;those who were responsible for the evaluation of any study end point were unaware of whether vaccine or placebo had been administered.&quot;</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Approximately 12% of subjects enrolled withdrew from TVC. Data collected until date of withdrawal/last contact were used for analysis.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>Reporting of efficacy outcomes using the mTVC was made more comprehensive with complete TVC numbers for many (but not all) outcomes. Outcomes outlined in protocol are reported.</td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funded by GlaxoSmithKline.</td>
</tr>
</tbody>
</table>

### Study: Leroux-Roels 2012

#### Methods

Phase I/II, open-label, parallel-group, multi-centre RCT with staggered enrollment + extension study.
Single centre in Belgium.
Duration: 12 months in primary trial; 42 months in extension to follow older adults administered HZ/su vaccine who completed the primary trial.

#### Participants

\( n = 155 \): 20 healthy young adults (age 18-30), and 135 healthy older adults (age 50-70). Extension study: \( n = 34 \).
Women had to be surgically sterilized, at least 1 year post-menopausal, or if childbearing potential, abstinent or using adequate contraception for 30 days prior to vaccination and have a negative pregnancy test.

Excluded if:
- taking immunosuppressants > 14 days or other immune-modifying agents within 6 months.
- received immunoglobulins/blood products within 3 months.
- received a vaccine (excludes influenza vaccine) ≤ 30 days of first dose of study vaccine(s).
- Had previously received a VZV vaccine.
- Had previously received a vaccine containing MPL or QS21.
- Had a history of HZ within the previous 5 years.
- Had known exposure to VZV within the previous 2 years.
- Had any contradiction to vaccination (such as allergy).
- Had acute disease at enrollment.

Excluded from extension study if:
- receiving immunomodulatory treatments or had an immunosuppressive or immunodeficient condition.
- previously received a vaccine against HZ.
- previously received a vaccine containing MPL or QS21.

### Interventions

**Young adults:**
2 doses, 2 months apart (months 0,2) of:
1. Recombinant subunit zoster vaccine 50 μg gE/AS01B, 0.5 mL IM (n = 10)
2. Recombinant subunit zoster vaccine 50 μg gE/AS01B, 0.5 mL IM + OKA 0.5 mL SC (n = 10)

**Older adults:**
2 doses, 2 months apart (months 0,2) of:
1. OKA (attenuated VZV approx 104 PFU in 0.5 mL diluent) SC (n = 45)
2. Recombinant subunit zoster vaccine 50 μg gE/AS01B, 0.5 mL IM (n = 45)
3. Recombinant subunit zoster vaccine 50 μg gE/AS01B, 0.5 mL IM + OKA 0.5 mL SC (n = 45)

### Outcomes
- Solicited local reactions (pain, redness, and swelling at injection site): recorded by subjects on diary cards up to 6 days after vaccination.
- Solicited general reactions (fatigue, fever, myalgia, gastrointestinal symptoms, and headache): recorded by subjects on diary cards for up to 6 days after vaccination.
- Unsolicited AEs: recorded by investigators until 30 days after each vaccination.
- Frequencies of gE-specific CD4 T cells with at least two antigen-specific cytokines (IFN-γ, IL-2, TNF-α, CD40L): At months 12, 30 and 42 after the first vaccination.
- Frequencies of VZV-specific CD4 T cells with at least two antigen-specific cytokines (IFN-γ, IL-2, TNF-α, CD40L): At months 12, 30 and 42 after the first vaccination.
- Frequencies of gE-specific CD4/CD8 T cells with antigen-specific IFN-γ and/or IL-2 and/or TNF α and/or CD40L secretion/expression: At months 12, 30 and 42.
- Frequencies of VZV-specific CD4/CD8 T cells with antigen-specific IFN-γ and/or IL-2 and/or TNF α and/or CD40L secretion/expression: At months 12, 30 and 42.
- Anti-gE-Ab concentrations: At months 12, 30 and 42.
- Anti-VZV Ab concentrations: At months 12, 30 and 42.
- Frequencies of gE-specific memory B cells: At months 30 and 42
- Frequencies of VZV-specific memory B cell: At months 30 and 42.
- Occurrence of SAEs: During primary study (up to month 12), and from last visit of primary study to month 42.
- Occurrence of clinically diagnosed HZ episodes: From last visit (Month 12) of primary study to month 42.

### Notes

<table>
<thead>
<tr>
<th>Risk of Bias</th>
<th>Bias</th>
<th>Authors/ Judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Method for randomization not described.</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Methods for allocation to treatment group not described.</td>
<td></td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>High risk</td>
<td>Open-label study.</td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Open-label study.</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>Primary study followed all enrolled patients; extension study excluded approximately 66% of originally eligible patients at month 42.</td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
<td>No protocol/registry data located regarding primary study. Reporting of registry-specified outcomes complete in extension study.</td>
<td></td>
</tr>
<tr>
<td>Other bias</td>
<td>High risk</td>
<td>Funded by GlaxoSmithKline.</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 4: Summary of Subject Withdrawals from ZOE-50 and ZOE-70, by Study Visit

<table>
<thead>
<tr>
<th></th>
<th>ZOE-50</th>
<th>ZOE-70</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ/su n (% TVC remaining)</td>
<td>Placebo n (% TVC remaining)</td>
</tr>
<tr>
<td>Visit 1 (Month 0)</td>
<td>7695 (100%)</td>
<td>7710 (100%)</td>
</tr>
<tr>
<td>Visit 2 (Month 2)</td>
<td>7520 (97.7%)</td>
<td>7561 (98.1%)</td>
</tr>
<tr>
<td>Visit 3 (Month 3)</td>
<td>7475 (97.1%)</td>
<td>7526 (97.6%)</td>
</tr>
<tr>
<td>Visit 4 (Month 14)</td>
<td>7337 (95.3%)</td>
<td>7375 (95.7%)</td>
</tr>
<tr>
<td>Visit 5 (Month 26)</td>
<td>7183 (93.3%)</td>
<td>7232 (93.8%)</td>
</tr>
<tr>
<td>Visit 6 (Month 38)</td>
<td>7063 (91.8%)</td>
<td>7120 (92.3%)</td>
</tr>
<tr>
<td>Study Conclusion</td>
<td>6773 (88.0%)</td>
<td>6808 (88.3%)</td>
</tr>
</tbody>
</table>

Data as retrieved from ZOE-50 and ZOE-70 CSRs
Appendix 5: Summary of HZ Case Diagnoses Decisions (via PCR, HZAC)

<table>
<thead>
<tr>
<th></th>
<th>ZOE-50 (TVC) HZ Cases</th>
<th>ZOE-70 (TVC) HZ Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ/su n = 96</td>
<td>Placebo n = 382</td>
</tr>
<tr>
<td>PCR confirmed (+ or –)</td>
<td>72 (75%)</td>
<td>294 (77%)</td>
</tr>
<tr>
<td>HZAC</td>
<td>24 (25%)</td>
<td>88 (23%)</td>
</tr>
</tbody>
</table>

**Final Diagnosis**

<table>
<thead>
<tr>
<th></th>
<th>ZOE-50 (TVC): HZ Cases</th>
<th>ZOE-70 (TVC): HZ Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ/su Placebo RR (95% CI)</td>
<td>HZ/su Placebo RR (95% CI)</td>
</tr>
<tr>
<td>TVC</td>
<td>12/7698 (0.16%)</td>
<td>280/7710 (3.6%)</td>
</tr>
<tr>
<td>WORST CASE</td>
<td>34/7698 (0.44%)</td>
<td>247/7710 (3.2%)</td>
</tr>
</tbody>
</table>

Data as retrieved from ZOE-50 and ZOE-70 CSRs
Appendix 6: HZ Incidence by Subgroup: Pooled data from ZOE-50 and ZOE-70

<table>
<thead>
<tr>
<th>HZ Incidence by Age</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ/su</td>
<td>Placebo</td>
<td>ARR</td>
</tr>
<tr>
<td>50-59</td>
<td>0.11%</td>
<td>3.08%</td>
<td>2.97%</td>
</tr>
<tr>
<td>60-69</td>
<td>0.27%</td>
<td>4.37%</td>
<td>4.1%</td>
</tr>
<tr>
<td>≥70</td>
<td>0.37%</td>
<td>3.53%</td>
<td>3.16%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HZ Incidence by Year</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HZ/su</td>
<td>Placebo</td>
<td>ARR</td>
</tr>
<tr>
<td>Year 1</td>
<td>0.05%</td>
<td>0.87%</td>
<td>0.82%</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.06%</td>
<td>1.18%</td>
<td>1.12%</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.1%</td>
<td>0.97%</td>
<td>0.87%</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.09</td>
<td>0.90%</td>
<td>0.81%</td>
</tr>
</tbody>
</table>

Data as retrieved from ZOE-50 and ZOE-70 CSRs