Synopsis for study ZOSTER-002 (115523)

Name of the finished product:
Shingrix®

Name of active substances:

Varicella-Zoster-Virus[1]-Glykoprotein-E-Antigen[2],[3]
50 Mikrogramm

[1]Varicella-Zoster-Virus = VZV

[2]adjuvantiert mit AS01B; dieses enthält:
Pflanzenextrakt aus *Quillaja saponaria* Molina, Fraktion 21 (QS-21)
50 Mikrogramm
3-*O*-Desacyl-4'-monophosphoryl-Lipid A (MPL) aus *Salmonella Minnesota*
50 Mikrogramm

[3]Glykoprotein E (gE) hergestellt in immortalisierten Ovarialzellen des chinesischen Hamsters (CHO-Zellen) mittels rekombinanter DNA-Technologie

Pharmaceutical entrepreneur:
GlaxoSmithKline Biologicals s.a.
Rue de l'Institut 89
B-1330 Rixensart,
Belgien

SYNOPSIS

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Study No.: 115523 (ZOSTER-002)

Title of the study:
A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' herpes zoster gE/AS01$_B$ candidate vaccine when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients.

This report provides all final vaccine efficacy (VE) data from the ZOSTER-002-analyses, including Quality of Life (QoL) data, and reactogenicity/safety data as well as humoral and cell-mediated immunogenicity data, obtained for HZ/su, previously referred to as gE/AS01$_B$. Correlate of protection (CoP) analysis will be presented in a future report.

Investigators and study centers:
Multicenter study conducted in 28 countries: Australia, Belgium, Bulgaria, Canada, Czech Republic (Czechia), Estonia, Finland, France, Germany, Greece, Hong-Kong, Israel, Italy, Japan, Malaysia, the Netherlands, New Zealand, Panama, Poland, Romania, Republic of Korea, Russian Federation, South Africa, Spain, Taiwan, Turkey, United Kingdom and United States (US).

The following Principal Investigators involved in this study reviewed the Clinical Study Report (CSR): Dr. Gaidano, SCDU (Struttura Complessa a Direzione Universitaria) di Ematologia, Azienda Ospedaliera Universitaria Maggiore di Novara,, Italy; Dr. de la Serna, Hospital Universitario 12 de Octubre, Madrid, Spain; Dr. Quittet, Centre Hospitalier Régional Universitaire de Montpellier - Hôpital Saint Eloi, France; Dr. Issa, Massachusetts General Hospital and Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, US; Dr. Chou, Niigata Cancer Center Hospital, Niigata, Japan.

Publication (reference): None at the time of this report.

Study period: **Study initiation date:** 13 July 2012 **Study completion date:** 01 February 2017 **Data lock point (Date of database freeze):** 05 September 2017	**Phase:** III

Indications: Prevention of HZ and related complications in adults ≥ 50 years of age (YOA) and immunocompromised adults ≥ 18 YOA.

Objectives:

Primary:

- To evaluate VE in the prevention of HZ in autologous HCT recipients 18 YOA and older.

  Criterion used: Clinically meaningful overall HZ VE was demonstrated if the lower limit (LL) of the 95% confidence interval (CI) was above 0%.

Secondary:

- To evaluate VE in reducing the total duration of 'worst' HZ-associated pain over the entire pain reporting period in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in the reduction of confirmed HZ-associated complications in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the prevention of post-herpetic neuralgia (PHN) in autologous HCT recipients 18 YOA and older;
- To evaluate humoral immune responses to the study vaccine, when administered according to a 2-dose schedule in a sub-cohort of subjects;
- To evaluate vaccine safety and reactogenicity in autologous HCT recipients 18 YOA and older.

Tertiary:

- To evaluate VE in the prevention of HZ in autologous HCT recipients 18 YOA and older when all subjects reach 1 year post-HCT;

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- To evaluate VE in the prevention of PHN in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in reducing the severity of acute HZ-associated pain in HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in improving QoL in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in the reduction of overall mortality in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the reduction of HZ-related mortality in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the reduction of overall hospitalizations in autologous HCT recipients 18 YOA and older*;
- To evaluate VE in the reduction of HZ-related hospitalizations in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the reduction in duration of pain medications in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate cell-mediated immune response to the study vaccine in a sub-cohort of subjects;
- To assess correlation of vaccine-induced humoral immune responses with protection against HZ**.

*This assessment was not performed but descriptive safety tables and serious adverse event (SAE) listings were provided.

**Data regarding CoP assessment are planned to be presented in a future report.

Methodology:

This was a phase III, observer-blind randomized, placebo-controlled, multi-center, multi-country study with two parallel groups to evaluate the efficacy of HZ/su, when administered intramuscularly on a 0 and 1 to 2 months schedule, in the prevention of HZ in autologous HCT recipients 18 YOA and older.

The first vaccination visit at Month 0 (Visit 1) was preceded by a Pre-vaccination visit that took place from 110 days prior to Visit 1 up to the day of Visit 1 (the Pre-vaccination visit could occur on the same day as Visit 1).

Eligible subjects were randomized to HZ/su or placebo according to a 1:1 ratio (*HZ/su was previously referred to as gE/AS01$_B$*).

The randomization algorithm used a minimization procedure accounting for different factors: age (18-49 YOA and ≥ 50 YOA), underlying-disease characteristics (subjects with an underlying diagnosis of multiple myeloma and all other diagnoses for which the HCT was undertaken), post-transplant antineoplastic therapy (subjects undergoing antineoplastic maintenance therapy with bortezomib at the time of first vaccination and subjects not undergoing antineoplastic maintenance therapy with bortezomib at the time of first vaccination, even if receiving another antineoplastic therapy), anticipated duration of post-transplant antiviral prophylaxis (duration of post-transplant antiviral prophylaxis up to and including 3 months [including subjects who as per standard of care did not receive any antiviral prophylactic therapy] and duration of post-transplant antiviral prophylaxis from more than 3 months up to and including 6 months), center, and gender. Overall, target enrolment was approximately 1063 subjects receiving HZ/su and approximately 1063 subjects receiving a placebo.

For female subjects of childbearing potential, a urine pregnancy test was performed at Visit 1 (Month 0) and Visit 2 (Month 1, i.e., 1 to 2 months after Visit 1). A serum pregnancy test at Visit 1 or Visit 2 was performed if required per local or ethics committee regulation.

Study staff provided subjects a diary card after each vaccination for daily recording of solicited symptoms (Days 0 to 6) and unsolicited symptoms (Days 0 to 29).

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SAEs and potential immune-mediated diseases (pIMDs) were collected and recorded from the first receipt of study vaccine/placebo up to Visit 4 (Month 13). Fatal SAEs were collected and recorded from the Pre-vaccination visit until study end. SAEs that were related to the investigational product were collected and recorded from the time of the first receipt of study vaccine/placebo (Visit 1, Month 0) until study end. Any relapse, i.e., a recurrence of the underlying malignancy or disease for which the HCT was undertaken, was to be recorded, from Visit 1 (Month 0) until study end. Pregnancies were to be reported from Month 0 until study end.

Blood samples were collected from all subjects at Visits 1 (pre-vaccination, Month 0) and 3 (post-second vaccination, Month 2) to possibly contribute to the CoP assessment.

Additionally, blood samples were collected from a subset of subjects (the Humoral Immunogenicity sub-cohort) at post-first vaccination at Visit 2 (Month 1), and post-second vaccination at Visit 4 (Month 13) and Visit 5 (Month 25) to assess persistence of humoral immune response. In these subjects, blood samples were also collected at Visit 1 and 3 to assess for humoral immune response.

Blood samples were collected from a sub-cohort of subjects (i.e., the cell-mediated Immunogenicity [CMI]-sub-cohort) at Visits 1, 2, 3, 4 and 5 to assess CMI responses. The CMI sub-cohort was a subgroup of the Humoral Immunogenicity sub-cohort.

After Visit 3, monthly contacts between the subjects and the investigator and/or his delegate took place to collect information on any event of interest that might have occurred. The contacts were not to take place at months that coincided with the subject's scheduled study visits (i.e., Visit 4 and 5).

In case of a suspected HZ episode, the subject had to complete a HZ-specific diary card and questionnaires and had additional visits and contacts for follow-up of HZ.

Whenever possible, rash lesion samples were collected from subjects clinically diagnosed as having a suspected case of HZ with characteristic HZ or VZV rash (HZ according criterion 1). A suspected case of HZ could be confirmed by polymerase chain reaction (PCR), or by the HZ Ascertainment Committee (HZAC, referred to as HZ Adjudication Committee in the HZAC charter, version 1, dated 04 October 2012, on file at GSK Biologicals). All suspected HZ cases were referred to the HZAC in a blinded manner. The HZAC classified these cases as either "HZ", "not HZ" or "not able to decide" (note that the protocol did not specify the "not able to decide" category). However, the HZAC classification served as the final case definition only when the case could not be confirmed or excluded by PCR; e.g., when all samples from a given subject were inadequate (as when both VZV and β-actin PCR results were negative), or when no samples were available for a given subject. Therefore, definitive PCR results, when available, determined the final HZ case assignment. If the case could not be confirmed or excluded by PCR and the HZAC final outcome was 'not able to decide', the overall final outcome was 'No possible classification'; for analysis the categories 'not HZ' and 'No possible classification' were considered as 'not HZ'. PCR test results or HZAC classification as described above would not have served as the final case definition if the following applied: cases of suspected HZ were not considered a confirmed case of HZ for the efficacy analysis if they potentially could constitute a primary VZV infection.

Cases of HZ with characteristic VZV or HZ rash and PHN associated with a case of HZ were to be recorded from Month 0 until study conclusion in HZ-specific screens. Any pre-defined HZ complication (different from PHN) was to be recorded, from Month 0 until study end, on an SAE or AE screen as appropriate. Cases of HZ without characteristics VZV or HZ rash (HZ according criterion 2) were to be recorded from Month 0 until study end on an SAE screen, and were to be specified there as related to HZ.

Zoster Brief Pain Inventory (ZBPI) questionnaires were completed to assess HZ-associated pain (broadly defined to include allodynia, pruritus or other sensations) and discomfort during an HZ episode and the impact of HZ on subject's QoL. PHN cases identified based on ZBPI reporting were considered for statistical analyses.

QoL questionnaires Euro-QoL 5 Dimension (EQ-5D) and Short form-36 (SF-36) were completed by all subjects at Visits 1, 3 and 4 and in case of suspected HZ.

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An Independent Data Monitoring Committee (IDMC) was appointed to monitor and follow-up the safety and tolerability of HZ/su. Unblinded evaluation of the safety data (with coded group names) was performed by the IDMC on an ongoing basis. The IDMC met periodically during the trial to review safety data and make recommendations regarding continuation, modification or discontinuation of the study following each meeting. The IDMC concluded after each review that the trial could continue as planned.

Study end was triggered on 04 November 2016 when the conditions for final triggered analysis were met (i.e., there were at least 125 confirmed HZ cases in the primary cohort for efficacy and all subjects had completed Visit 4 [Month 13]). Data contributing to the analysis of the primary efficacy objective (HZ cases) were collected until the cut-off date (04 November 2016). Conclusion visits took place after the cut-off date for final triggered analysis. Between the cut-off date and conclusion visits, safety data continued to be collected until study conclusion. In addition, each suspected HZ case ongoing at the time of the cut-off date for final triggered analysis, was followed for at least 90 days to allow accurate diagnosis of PHN. Study end (last subject last visit) occurred on 01 February 2017. All data (except the data regarding CoP assessment) accrued up to study end were included in the analysis and are presented in the study report.

Study vaccine and comparator, dose, mode of administration, lot no.:

Vaccination schedule/site:

HZ/su group subjects received 2 doses of HZ/su.

Placebo group subjects received 2 doses of placebo.

For both groups, the first dose was administered at Visit 1 and the second dose at Visit 2 (1 to 2 months after the first dose) through intramuscular injection into the deltoid muscle of the non-dominant arm. In rare situations when there was no alternative, the injection could be given in the other arm.

Study vaccine and comparator composition/dose/lot number:

Treatment name	Product name*	Formulation	Presentation	Volume to be administered	Lot numbers
HZ/su	VZV gE	50 μg gE per 0.5 mL of reconstituted vaccine	Lyophilized pellet in a monodose vial	0.5 mL	DVZVA007A, DVZVA008A, DVZVA007B
	$AS01_{B}$*	MPL, QS21 and liposome (50 μg MPL and 50 μg QS21) per 0.5 mL of reconstituted vaccine	Liquid in a monodose vial		DA01A052A, DA01A055A, DA01A050A
Placebo	Lyophilized sucrose cake	20 mg sucrose per 0.5 mL of reconstituted placebo	Lyophilized pellet in a monodose vial	0.5 mL	PVZVA003A, PVZVA005A
	Saline (NaCl) solution for reconstitution	150 mM NaCl solution (water for injection)	Liquid in a monodose vial		DD02A009, DD02A011A

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified Glycoprotein E; $AS01_{B}$ = Adjuvant System $AS01_{B}$; NaCl = Sodium Chloride; MPL = 3-O-desacyl-4'-monophosphoryl lipid A; QS21 = *Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)

*Components of the reconstituted study vaccine HZ/su (referred in the protocol to as $gE/AS01_{B}$) and placebo, respectively.

Study Population:

Male and female subjects at least 18 years old (and having reached the age of local legal consent) at the time of study entry, who had provided informed consent, had undergone or were to undergo autologous HCT within 50-70 days prior to the first vaccination with the study vaccine/placebo, and with, at study entry, no planned additional HCTs (tandem autologous HCT recipients could participate following their final HCT).

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Female subjects were to be of non-childbearing potential or were to practice adequate contraception for a minimum of 30 days prior to vaccination to be continued through 12 months post-study vaccinations and to have a negative pregnancy test before each vaccination dose.

Subjects receiving prophylactic antiviral therapy (with activity against VZV) expected to last more than 6 months after transplantation were excluded. Subjects having a varicella or HZ episode by clinical history or a varicella or HZ vaccination within the 12 months preceding the first study vaccination were excluded, as well as subjects who had planned to receive during the study a HZ vaccine (including an investigational or non-registered vaccine) other than the study vaccine.

Duration of treatment:

The exact study duration varied between subjects. Each subject was to be followed at least until he/she completed Visit 4 (i.e., until Month 13), approximately 12 months after the second dose of study vaccine/placebo, and there were at least 125 confirmed HZ cases in the primary cohort for efficacy (cut-off date final triggered analysis: 04 November 2016).

Once conditions for final triggered analysis were met, the conclusion visit was to take place. Any remaining monthly contacts after Visit 4, Visit 5, and monthly contacts after Visit 5 were not to take place. Each suspected HZ case ongoing at the cut-off date for final triggered analysis was to be followed for at least 90 days. The maximal study duration recorded in the study for a subject was approximately 4 years.

Criteria for evaluations:

Primary endpoint:

- Occurrence of confirmed HZ cases
  - Incidence of confirmed HZ cases from Month 0 until study end.

Secondary endpoints:

- Duration of 'worst' HZ-associated pain
  - Duration of HZ-associated pain rated as 3 or greater on the 'worst pain' ZBPI question, following the onset of a confirmed HZ rash over the entire pain reporting period in subjects with confirmed HZ;
- Occurrence of confirmed HZ-associated complications
  - Incidence of confirmed HZ complications following the onset of HZ from Month 0 until study end;
- Occurrence of PHN
  - Incidence of PHN from Month 0 until study end;
- Antigen-specific antibody (Ab) concentrations in a sub-cohort of subjects
  - Anti- gE Ab concentrations as determined by ELISA in a sub-cohort of subjects at Month 0, Month 1, Month 2, Month 13 and Month 25;
- Occurrence of solicited local and general symptoms
  - Occurrence and intensity of each solicited local symptom within 7 days (Days 0-6) after each vaccination in all subjects;
  - Occurrence, intensity and relationship to vaccination of each solicited general symptom within 7 days (Days 0-6) after each vaccination, in all subjects;
- Occurrence of unsolicited adverse events (AEs)
  - 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;
- Occurrence of SAEs
  - Occurrence and relationship to vaccination of all SAEs from Month 0 until Month 13 in all subjects;

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- Occurrence of SAEs related to the GSK study vaccine/placebo from Month 0 until study end in all subjects;
- Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine from the Pre-vaccination visit until study end in all subjects;
- Occurrence of any fatal SAEs from the Pre-vaccination visit until study end in all subjects;

- Occurrence of AEs of specific interest
  - Occurrence and relationship to vaccination of any pIMD from Month 0 until Month 13 in all subjects;
  - Occurrence of relapse cases from Month 0 until study end in all subjects.

Relapse: recurrence of the underlying malignancy or disease for which the HCT was undertaken.

Tertiary endpoints:

- Occurrence of confirmed HZ cases in subjects having at least 1 year post-HCT
  - Incidence of confirmed HZ cases in subjects having at least 1 year post-HCT;
- Occurrence of PHN in subjects with confirmed HZ
  - Incidence of PHN from Month 0 until study end in subjects with confirmed HZ;
- Acute HZ severity
  - Acute HZ severity as determined by the mean Area Under Curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-week period following the onset of confirmed HZ in subjects with confirmed HZ;
- Interference of HZ with QoL
  - Interference of HZ with QoL as measured by ZBPI in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by EQ-5D in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by SF-36 in subjects with confirmed HZ;
- Occurrence of overall mortality
  - Incidence of overall mortality from Month 0 until study end;
- Occurrence of HZ-related mortality
  - Incidence of HZ-related mortality from Month 0 until study end;
- Occurrence of overall hospitalizations*
  - Incidence of overall hospitalizations from Month 0 until study end;
- Occurrence of HZ-related hospitalizations
  - Incidence of HZ-related hospitalizations from Month 0 until study end;
- Duration of pain medication administered for HZ
  - Duration of pain medication administered for HZ from Month 0 until study end in subjects with confirmed HZ;
- CMI in terms of frequencies of antigen-specific CD4+ T-cells in a sub-cohort of subjects
  - Frequencies of CD4+ T-cells following induction with gE antigens, as determined by *in vitro* intracellular cytokine staining (ICS), expressing at least 2 activation markers (from among IFN-γ, IL-2, TNF-α and CD40L**) in a sub-cohort of subjects at Month 0, Month 1, Month 2, Month 13 and Month 25;
  - Frequencies of CD4+ T-cells following induction with gE antigens, as determined by *in vitro* ICS, expressing each individual activation marker in addition to one other marker (from among IFN-γ, IL-2, TNF-α and CD40L) in a sub-cohort of subjects at Month 0, Month 1, Month 2, Month 13 and Month 25;
- Antigen-specific Ab concentrations at Month 0 and at Month 2 in subjects with confirmed HZ***
  - Anti-gE Ab concentrations as determined by enzyme-linked immunosorbent assay (ELISA) at Month 0 and at Month 2, in all subjects with confirmed HZ compared to matched controls.

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*This analysis was not performed but descriptive safety tables and SAE listings were provided.

**IFN-γ = interferon gamma; IL-2 = Interleukin-2; TNF-α = Tumor Necrosis Factor alpha; CD40L = CD40 Ligand

***Data regarding CoP assessment will be presented in a future report.

Statistical methods:

- Analysis of demographics and other baseline characteristics

Demographic characteristics (age at first study vaccination, gender, geographic ancestry and ethnicity) were tabulated overall.

The cohorts description and withdrawal status from the study were summarized using descriptive statistics.

- Analysis of efficacy

The primary efficacy analysis was based on the modified Total Vaccinated Cohort (mTVC), which excluded subjects in the Total Vaccinated Cohort (TVC) analysis who were not administered with the second vaccination or who received vaccine doses /or replacement not on the same group or who developed a confirmed case of HZ prior to 1 month after the second vaccination.

Reduction in HZ risk

The primary analysis method of the VE considered the exact inference on the relative risk conditionally to the total number of HZ cases observed and time at risk.

This method computes an exact CI around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the sum of the time at risk of the subjects within each group.

Relative risk (RR) was defined as the ratio of the incidence rates of the HZ/su group over the Placebo group. VE = 1 – RR.

The time at risk for a subject was calculated from HZ onset to time zero relative to the cohort considered: from first vaccination for TVC and from 30 days following the second vaccination for mTVC and According to Protocol (ATP) cohort for efficacy. The number of Person-Years at risk was defined as the sum of the time at risk for all subjects at risk during, either up to the cut-off date for the analysis (04 November 2016), the censoring date (drop-out;) or the occurrence of the first HZ case for a subject.

In addition, subjects with relapse of the original malignancy or disease for which the HCT was undertaken were censored from the mTVC and ATP analysis from the date that they started the therapy to treat relapse.

Reduction in overall PHN and HZ associated complications risks

The overall reduction in PHN risk was evaluated similarly to the HZ risk using the exact inference on the RR conditionally to the total number of PHN cases observed and time at risk. PHN was defined by the presence of HZ-associated severe “worst” pain persisting or appearing more than 90 days after onset of the HZ rash. For this analysis, severe “worst” pain was defined as HZ-associated pain rated as 3 or greater on the “worst pain” ZBPI question.

The same approach was used to analyses the reduction in the risk of HZ-associated complications.

Reduction in PHN incidence in subjects with an HZ episode

The incidence of PHN, in subjects with an HZ episode, was presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985].

Reduction of duration of ‘worst’ pain in subjects with an HZ episode and duration of pain medications

The analysis of duration of ‘Worst pain’ involved any subject reporting ZBPI pain scores of 3 or more at any time during the study. The time-to-cessation of severe ‘worst’ pain was analyzed using a survival methodology. Cox -proportional model was used to assess the hazard rate reduction in ZBPI worst pain duration due to the vaccine in those subjects that presented HZ. The same approach was used to analyze the reduction in the duration of pain medications.

The use of pain medication, in subjects with an HZ episode was compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985].

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Reduction in overall mortality and HZ-associated mortality and hospitalization

The analysis of (overall and HZ associated) mortality was based using Cox's proportional hazard regression using age group, underlying diseases and the anticipated duration of post-transplant antiviral prophylaxis factors with vaccine groups as covariates. VE was then calculated as 1 minus the hazard ratio. A similar approach was used for the analysis of HZ-related hospitalizations.

- Analysis of Quality of Life

Analysis of Quality of Life by ZBPI

The severity of HZ-Pain was measured from the ZBPI worst pain score at Days 30, 90 and 182 using AUC methods. The mean pain was compared across vaccine groups using the non-parametric Wilcoxon test. Time to resolution of clinically significant pain was analyzed for the HZ ZBPI evaluable subgroup. An event was defined as having a worst pain score < 3 for a documented 4-week clinically significant pain-free period. Time-to-event curves were estimated using the Kaplan-Meier method. A log rank test was used to compare vaccine groups.

The HZ severity-of-illness score and HZ burden-of-illness scores were calculated from the ZBPI worst pain scores and the HZ severity-of-interference score and HZ burden-of-interference score were calculated from the ZBPI Activities of Daily Living (ADL) score, over the 182 days from the first day of HZ rash (HZR Day0) using AUC methods. The burden and severity scores were calculated based on the mTVC. The scores were defined as 0 for participants who did not develop an evaluable case of HZ during the study. Subjects who had a confirmed HZ episode but did not complete any ZBPI assessments were considered missing for this analysis.

Analysis of Quality of Life using SF-36 and EQ-5D

Data for HZ cases were analyzed using (a) descriptive statistics, (b) repeated measures analysis of variance and (c) a multivariate Rank Analysis of repeated measures ordinal categorical for the multi-item SF-36 and EQ-5D scales for each vaccine group.

Estimation of HZ impact on utility score: A model was fitted to estimate the HZ impact on both the EQ-5D and SF-36 utility scores in the Placebo group only stratified by age. The model included the baseline utility scores, i.e., most recent pre-HZ assessment (at one of Months 0, 2 or 13) and the utility scores during the first four weeks of the HZ episode.

- Analysis of humoral immunogenicity

The primary analysis was based on the ATP cohort for analysis of humoral immunogenicity which included all evaluable subjects planned in the humoral immunogenicity sub-cohort and meeting protocol requirements for the inclusion in the ATP cohort for humoral immunogenicity.

The analysis method of the post-vaccination log-transformed immunogenicity marker data at Month 2 used a likelihood-based model with repeated measurements (including Month 1 and Month 2). The fixed-effect model included the means for two levels of the treatment effect and adjusted for age strata and underlying diseases. The pre-vaccination log-transformed values were included as continuous covariate. For each group, adjusted means and difference of means between treatment groups were calculated together with 95% CIs (2-sided) and back-transformed to the original units to provide geometric means (GMs) and GM ratios.

- Analysis of CMI

The primary analysis was based on the ATP cohort for analysis of CMI which included all evaluable subjects planned in the CMI sub-cohort and meeting protocol requirements for the inclusion in the ATP cohort for CMI. The primary evaluation of the vaccine on CMI endpoint was based on treatment group comparison in the frequency of gE-specific CD4+ T-cell secreting at least 2 activation markers among IL-2, IFN-γ, TNF-α, and CD40L (i.e., CD4 [2+] T-cell frequency). A likelihood-based Analysis of Covariance (ANCOVA) model with repeated measurement (including Month 1 and Month 2) was used to analyze the log-transformed ratio between induction frequency and background frequency of CD4[2+]. The fixed-effect model included the means for two levels of the treatment group effect. The age strata and underlying diseases were included in the model.

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The continuous covariates included: the pre-vaccination log-transformed CD4[2+] T-cell frequency following induction with gE and the post-vaccination log-transformed CD4+ T-cell frequency under background condition. Least-square means and difference of least-squares means were then back-transformed and used to provide estimates for the frequency difference divided by background ([induction – background] / background). Primary timepoint is Month 2.

- Analysis of safety

The primary analysis was based on the TVC which included all vaccinated subjects with respect to the vaccine actually administered. The percentage of subjects reporting each individual solicited local and general AE during the solicited 7-day-follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 1 and above, grade 2 and above and grade 3 solicited AEs and for solicited general AEs with relationship to vaccination. The proportion of subjects with at least one report of unsolicited AE classified by the MedDRA Preferred Terms and reported up to 30 days after each vaccination was tabulated with exact 95% CI. The same tabulation was performed for grade 3 unsolicited AEs, for unsolicited AEs with a relationship to vaccination and for unsolicited AEs with medically attended visit. SAEs and pIMDs reported up to 365 days post-last vaccination were tabulated. Withdrawals due to (S)AEs up to Visit 5 were tabulated, and withdrawals due to fatal SAEs from after Visit 5 up to cut-off date. Fatal SAEs, SAEs considered related as per investigator assessment and relapses from first vaccination up to study end were tabulated.

Synopsis Table 1: Study population (Total vaccinated cohort)

Number of subjects	**HZ/su**	**Placebo**
Planned, N	1063	1063
Randomised, N (Total Vaccinated Cohort)	922	924
Completed, n (%)	694 (75.3)	672 (72.7)
Demographics	**HZ/su**	**Placebo**
N (Total Vaccinated Cohort)	922	924
Females:Males	342:580	346:578
Mean Age, years (SD)	54.8 (11.7)	55.1 (11.4)
Median Age, years (minimum, maximum)	57 (18, 78)	58 (18, 75)
White - Caucasian / European Heritage, n (%)	715 (77.5)	712 (77.1)
Asian - East Asian Heritage, n (%)	83 (9.0)	91 (9.8)
Asian - Japanese Heritage, n (%)	43 (4.7)	38 (4.1)

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
Completed = until 04 November 2016 (subjects with a study conclusion date on or after the cut-off date for final analysis [04 November 2016])
Note: The 3 most frequent geographic ancestries are presented in the table. Geographic ancestries occurring less frequently (< 4.1% of subjects in the HZ/su and Placebo groups, respectively) were the following: African Heritage / African American, American Indian or Alaskan Native, Asian - Central/South Asian Heritage, Asian - South East Asian Heritage, White - Arabic / North African Heritage, Other.
Of note between the cut-off date for final analysis (4 November 2016) until study conclusion, 6 subjects (3 in each group) incurred a fatal outcome.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Summary:

Except for the analyses of the primary endpoint, all the other analyses (of secondary and tertiary endpoints including by subgroup analyses) were exploratory. The study was not designed to draw confirmatory conclusions on these analyses as no control of type I error was done.

Efficacy results:

Primary objective:

HZ VE in autologous HCT recipients ≥ 18 YOA (mTVC)

In the primary HZ VE (first or only episode of HZ) analysis on mTVC, a total of 184 subjects reported at least one confirmed HZ episode, amongst which 49 were in the HZ/su group and 135 in the Placebo group. All confirmed HZ episodes were cases of HZ with characteristic VZV or HZ rash (HZ according criterion 1). The median follow-up time was approximately 21 months; with approximately 22 months in the HZ/su group and approximately 20 months in the Placebo group.

The overall HZ VE (first or only episode of HZ) was 68.17% (95% CI: 55.56% - 77.53%; P<0.0001). The primary objective of the study was met since the LL of the 95% CI was above 0% (see Synopsis Table 2).

Subgroup analyses of HZ VE:

- HZ VE by age strata:
  - 18-49 YOA: 71.77% (95% CI: 38.75% - 88.25%)
  - ≥ 50 YOA: 67.34% (95% CI: 52.60% - 77.89%)
- HZ VE by underlying diseases:
  - Multiple myeloma: 72.35% (95% CI: 54.76% - 83.71%)
  - Other diagnoses: 63.63% (95% CI: 42.29% - 77.66%)
- HZ VE by gender:
  - Female: 77.60% (95% CI: 60.66% - 87.95%)
  - Male: 60.28% (95% CI: 39.37% - 74.48%)

Note:

The results obtained on the TVC and ATP cohort for efficacy were in line with results obtained on the mTVC.

Synopsis Table 2: Vaccine efficacy: First or only episode of HZ during the entire study period using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				Placebo					95% CI		
Type	N	n	T (year)	n/T (per 1000)	N	n	T (year)	n/T (per 1000)	(%)	LL	UL	p-value
OVERALL	870	49	1633.1	30.0	851	135	1431.9	94.3	68.17	55.56	77.53	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
N = number of subjects included in each group
N = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years
n/T (per 1000) = Incidence rate of subjects reporting at least one event
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine Efficacy (Poisson method)
P-value = Two sided Exact P-value conditional to number of cases

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Secondary objectives

Reduction of duration of severe 'worst' HZ associated pain in autologous HCT recipients ≥ 18 YOA with a confirmed HZ episode (mTVC):

The VE in subjects with a confirmed HZ episode in terms of reduction of duration of severe 'worst' HZ-associated pain was 38.53% (95% CI: 11.05% - 57.52%).

VE against HZ related complications in autologous HCT recipients ≥ 18 YOA (mTVC)

At least one HZ complication was observed in 3 out of 870 subjects of the HZ/su group and 13 out of 851 subjects of the Placebo group. Reported HZ complications were HZ meningoencephalitis (1 subject in the Placebo group) and HZ cutaneous disseminated (3 subjects in the HZ/su group and 12 subjects in the Placebo group).

The overall VE against HZ related complications during the entire study period was 77.76% (95% CI: 19.05% - 95.93%).

VE in the prevention of overall PHN in autologous HCT recipients ≥ 18 YOA (mTVC)

There were 10 subjects with PHN episodes, 1 was in the HZ/su group and 9 were in the Placebo group.

The overall PHN VE (first or only episode of PHN) during the entire study period was 89.27% (95% CI: 22.54% - 99.76%).

Tertiary objectives

HZ VE during 1 year post-HCT in autologous HCT recipients ≥ 18 YOA (mTVC)

The HZ VE during 1 year post-HCT (median follow-up time was 7.6 months, with 7.7 months in the HZ/su group and 7.6 months in the Placebo group) was76.15% (95% CI: 61.11% - 85.98%).

Reduction of PHN incidence in autologous HCT recipients ≥ 18 YOA with a confirmed HZ episode (mTVC)

In subjects with a confirmed HZ episode, PHN was reported in 1 out of 49 subjects of the HZ/su group and 9 out of 135 subjects of the Placebo group.

The VE in terms of reduction of PHN incidence in subjects with a confirmed HZ episode was 69.39% (95% CI: -77.38% - 94.97%).

Reduction of overall and confirmed HZ episode related mortality and confirmed HZ episode related hospitalizations in autologous HCT recipients ≥ 18 YOA (mTVC)

HZ-related mortality was not observed in the autologous HCT recipients ≥ 18 YOA.

HZ-related hospitalizations were observed in 2 subjects of the HZ/su group and 13 subjects of the Placebo group.

The VE against first or only episode of confirmed HZ episode related hospitalizations during the entire study period was 84.70% (95% CI: 32.15% - 96.55%).

Reduction in use and duration of HZ-associated pain medications in autologous HCT recipients ≥ 18 YOA with a confirmed HZ episode (mTVC)

In subjects with a confirmed HZ episode, 32 (65.31%) out of 49 subjects and 94 (69.63%) out of 135 subjects in the HZ/su group and the Placebo group, respectively, took at least one pain medication associated with HZ during the entire study period.

The VE in terms of reduction in use of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode was 6.21% (95% CI: -15.84% - 27.82%).

The VE in terms of reduction in duration of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode was 22.45% (95% CI: -15.85% - 48.09%).

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Quality of Life results:

A summary of the results of the QoL analyses is presented:

- Consistent differences were observed in favor of the HZ/su group compared to the Placebo group when measuring pain associated with the HZ episode using the ZBPI.
- The overall VE estimate for the ZBPI burden-of-illness score was 82.5% (95% CI: 73.6% - 91.4%). The overall VE estimate for the ZBPI burden-of-interference score was 82.8% (95% CI: 73.3% - 92.3%).
- The median time to resolution of clinically significant pain was 20 days in the HZ/su group and 31 days in the Placebo group.
- Consistent differences were observed in favor of the HZ/su group compared to the Placebo group in the AUC scores for the ZBPI worst pain score, ZBPI average pain score, and ZBPI ADL score for all of the time periods, i.e., 30, 90 and 182 days suggesting that the severity of disease was reduced in the HZ/su group compared with the Placebo group.
- Some differences were observed between HZ/su and Placebo groups, in favor of HZ/su, when analyzing the SF-36 and EQ-5D scales, particularly at Week 1 of the HZ episode. No consistent differences in favour of either group were observed at other timepoints suggesting that the largest differences between HZ/su and Placebo groups in the impact on QoL were observed in the first week of the HZ episode.
- The estimated HZ Disutility Score by age group and timepoint assessed using the EQ-5D in the Placebo Group was estimated as -0.3328 (95% CI: -0.4383, -0.2274) and -0.2406 (95% CI: -0.3035, -0.1778) on Day 0 in the age groups 18-49 YOA and ≥50 YOA, respectively suggesting a major impact on QoL due to the HZ episode for non-vaccinated subjects.

Immunogenicity results:

Humoral immunogenicity

Anti-gE specific humoral immune response overall

In autologous HCT recipients ≥ 18 YOA a strong anti-gE Ab response was elicited following a two dose-schedule of HZ/su (Month 2). From all timepoints evaluated, the highest immune responses were observed one month post-dose 2. The anti-gE Ab responses decreased one year post-dose 2 (Month 13) but persisted well above pre-vaccination levels for up to two years post-dose 2 (Month 25).

Post-vaccination, anti-gE GMCs at Months 1, 2, 13 and 25 were 1844.2 mIU/mL (95% CI: 1282.2 – 2652.4), 12753.2 mIU/mL (95% CI: 7973.0 – 20399.4), 3183.8 mIU/mL (95% CI: 1869.8 – 5421.2) and 2819.0 mIU/mL (95% CI: 1387.1 – 5729.1), respectively, for the HZ/su group. The MGI (versus Month 0) in the HZ/su group at Months 1, 2, 13 and 25 were 2.49 (95% CI: 1.78 – 3.49), 16.72 (95% CI: 10.01 – 27.92), 4.51 (95% CI: 2.58 – 7.89) and 4.35 (95% CI: 1.89 – 9.99), respectively. VRRs at Months 1, 2, 13 and 25 were 29.5% (95% CI: 19.7% - 40.9%), 67.1% (95% CI: 55.8% - 77.1%), 40.4% (95% CI: 27.0% - 54.9%) and 44.7% (95% CI: 28.6% - 61.7%), respectively. The adjusted GM ratio for HZ/su over placebo of anti-gE Ab concentrations at Month 2 was 21.56 (95% CI: 12.91 – 36.01) (Synopsis Table 3).

Synopsis Table 3: Adjusted geometric means and ratio for HZ/su over Placebo of anti-gE antibody ELISA concentrations at Month 2 (ATP cohort for Humoral-immunogenicity)

			Adjusted geometric mean			Adjusted geometric mean ratio			
				95% CI			95% CI		
Timing	**group**	**N**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**	**P-value for the ratio**
PII(M2)	HZ/su	82	11227.7	6769.6	18621.7	21.56	12.91	36.01	<.0001
	Placebo	76	520.7	470.0	577.0	.	.	.	.

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
N = number of subjects in a given category with available results
LL = Lower Limit, UL = Upper Limit and CI = Confidence Interval
Confidence Interval (CI) were back transformed to original units
The p-value is relative to the null hypothesis Ho: Vaccine / Placebo = 1
PII(M2) = Post-vaccination Dose II (Month 2)

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Anti-gE specific humoral immune response by subgroup

The results obtained for the 18-49 YOA and ≥ 50 YOA strata consistently showed high anti-gE immune responses in the HZ/su group that remained above pre-vaccination levels up to two years post-dose 2.

The results of the analyses by underlying diseases (subjects with an underlying diagnosis of multiple myeloma or with all other diagnoses [including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T-cell lymphoma, acute myeloid leukemia, solid organ malignancies, etc.]) in autologous HCT recipients ≥ 18 YOA consistently showed high anti-gE immune responses in the HZ/su group.

Cell-mediated immunogenicity

gE-specific CMI overall

In autologous HCT recipients ≥ 18 YOA, strong gE-specific CMI responses were observed following two doses of HZ/su at one month post-dose 2 (Month 2). The highest immune responses were observed at one month post-dose 2; the observed gE-specific CMI responses were lower one year post-dose 2 (Month 13) but persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25).

In the HZ/su group, the observed median (min - max) frequency of gE-specific CD4[2+] T-cells (per 10^6 total CD4+ T-cells) was 48.9 (1.0 – 2469.7), 570.3 (1.0 – 14121.1), 6644.9 (1.0 – 73143.3), 1706.4 (1.0 – 17462.0) and 2294.4 (52.0 – 26020.4) at Months 0, 1, 2, 13 and 25, respectively. In the Placebo group, at all timepoints the observed median frequency of gE-specific CD4[2+] T-cells remained at pre-vaccination levels (point estimate of 65.0 at Month 0).

In the HZ/su group, the observed median (min - max) fold increase over pre-vaccination in the frequency of gE-specific CD4[2+] T-cells was 8.2 (0.0 – 3486.5), 109.0 (0.0 – 24677.3), 43.6 (0.0 – 7502.6) and 50.9 (0.3 – 3126.4) at Months 1, 2, 13 and 25. In the Placebo group, the observed median fold increase over pre-vaccination in the frequency of gE-specific CD4[2+] T-cells (point estimate) was not higher than 2.1 at any timepoint.

In the HZ/su group, the VRR in the frequency of gE-specific CD4[2+] T-cells was 46.3% (95% CI: 30.7% - 62.6%), 92.9% (95% CI: 80.5% - 98.5%), 70.4% (95% CI: 49.8% - 86.2%) and 70.8% (95% CI: 48.9% - 87.4%) at Months 1, 2, 13 and 25. In the Placebo group, the VRR in the frequency of gE-specific CD4[2+] T-cells (point estimate) was not higher than 12.5% at any timepoint.

The exploratory group comparison at one month post-dose 2 (Month 2) showed a higher adjusted GM frequency of gE-specific CD4[2+] T-cells in the HZ/su group as compared to the Placebo group. The adjusted GM ratio (HZ/su group/Placebo group) was 64.36 (95% CI: 21.80 – 190.06) (Synopsis Table 4).

Synopsis Table 4: Adjusted geometric means and ratio of HZ/su over Placebo for gE-specific CD4[2+] T-cells frequencies at Month 2 (ATP cohort for Cell-Mediated Immunogenicity)

			Adjusted geometric mean			Adjusted geometric mean ratio			
				95% CI			95% CI		
Timing	**group**	**N**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**	**P-value for the ratio**
PII(M2)	HZ/su	42	5397.0	4013.7	7231.8	64.36	21.80	190.06	<.0001
	Placebo	41	83.9	5.3	189.4	.	.	.	.

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
N = number of subjects in a given category with available results
LL = Lower Limit, UL = Upper Limit and CI = Confidence Interval
Confidence Interval (CI) were back transformed to original units
The p-value is relative to the null hypothesis Ho: Vaccine / Placebo = 1
PII(M2) = Post-vaccination Dose II (Month 2)

gE-specific CMI by subgroup

The results obtained in the 18-49 YOA and ≥ 50 YOA strata consistently showed in the HZ/su group gE-specific CMI responses above pre-vaccination levels at one month post-dose 2 (Month 2) that persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25).

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

The results obtained in autologous HCT recipients ≥ 18 YOA by underlying diseases (subjects with an underlying diagnosis of multiple myeloma or with all other diagnoses [including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T-cell lymphoma, acute myeloid leukemia, solid organ malignancies, etc.]) consistently showed in the HZ/su group gE-specific CMI responses above pre-vaccination levels at one month post-dose 2 (Month 2) that persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25).

Safety results:

Overall

Any AEs during the 7-day (Days 0-6) post-vaccination period (dose 1 and dose 2 considered):

- Overall, at least one solicited or unsolicited AE (local or general) was reported for 88.8% and 57.1% of subjects in the HZ/su and Placebo groups, respectively.
- Overall, at least one grade 3 solicited or unsolicited AE (local or general) was reported for 22.2% and 6.8% of subjects in the HZ/su and Placebo groups, respectively.

Solicited local symptoms during the 7-day (Days 0-6) post-vaccination period (dose 1 and dose 2 considered):

- Overall, at least one solicited local symptom was reported for 85.8% and 10.4% of subjects in the HZ/su and Placebo groups, respectively. The most frequently reported solicited local symptom in the HZ/su group was pain: 83.9% of subjects versus 9.3% of subjects in the Placebo group (Synopsis Table 5).
  - After dose 1 and dose 2, respectively, at least one solicited local symptom was reported for 78.8% and 78.2% of subjects in the HZ/su group; and for 7.1% and 5.9% of subjects in the Placebo group.
- Overall, at least one grade 3 solicited local symptom was reported for 14.2% and 0.3% of subjects in the HZ/su and Placebo groups, respectively.
  - After dose 1 and dose 2, respectively, at least one grade 3 solicited local symptom was reported for 7.4% and 10.5% of subjects in the HZ/su group; and for 0.3% and 0.0% of subjects in the Placebo group.
- Regarding the duration of solicited local symptoms during the 7-day post-vaccination period, overall/dose, the median duration for pain was 3.0 days in the HZ/su group and 1.0 day in the Placebo group.

Synopsis Table 5: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period overall subjects and overall doses (Total Vaccinated Cohort)

		HZ/su					Placebo				
					95% CI					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/dose											
Pain	All	1736	1326	76.4	74.3	78.4	1724	101	5.9	4.8	7.1
	Grade 3	1736	122	7.0	5.9	8.3	1724	3	0.2	0.0	0.5
Redness (mm)	All	1736	418	24.1	22.1	26.2	1724	9	0.5	0.2	1.0
	>100	1736	31	1.8	1.2	2.5	1724	0	0.0	0.0	0.2
Swelling (mm)	All	1736	233	13.4	11.9	15.1	1724	10	0.6	0.3	1.1
	>100	1736	13	0.7	0.4	1.3	1724	0	0.0	0.0	0.2
Overall/subject											
Pain	All	901	756	83.9	81.3	86.2	892	83	9.3	7.5	11.4
	Grade 3	901	99	11.0	9.0	13.2	892	3	0.3	0.1	1.0
Redness (mm)	All	901	301	33.4	30.3	36.6	892	9	1.0	0.5	1.9
	>100	901	28	3.1	2.1	4.5	892	0	0.0	0.0	0.4
Swelling (mm)	All	901	168	18.6	16.2	21.3	892	9	1.0	0.5	1.9
	>100	901	13	1.4	0.8	2.5	892	0	0.0	0.0	0.4

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

Solicited general symptoms during the 7-day (Days 0-6) post-vaccination period (dose 1 and dose 2 considered):

- Overall, at least one solicited general symptom was reported for 75.2% and 50.9% of subjects in the HZ/su and Placebo groups, respectively. The most frequently reported solicited general symptoms in the HZ/su group were fatigue (56.4% versus 38.0% in the Placebo group) and myalgia (53.7% versus 26.2% in the Placebo group) (Synopsis Table 6). At least one solicited general symptom with causal relationship to vaccination as per investigator assessment was reported for 42.1% and 16.8% of subjects in the HZ/su and Placebo groups, respectively.
  - After dose 1 and dose 2, respectively, at least one solicited general symptom was reported for 59.2% and 66.0% of subjects in the HZ/su group; and for 41.9% and 36.8% of subjects in the Placebo group. After dose 1 and dose 2, respectively, at least one solicited general symptom with causal relationship to vaccination as per investigator assessment was reported for 26.5% and 34.6% of subjects in the HZ/su group; and for 11.8% and 10.2% of subjects in the Placebo group.
- Overall, at least one grade 3 solicited general symptom was reported for 13.2% and 6.0% of subjects in the HZ/su and Placebo groups, respectively. At least one grade 3 solicited general symptom with causal relationship to vaccination as per investigator assessment was reported for 7.8% and 1.0% of subjects in the HZ/su and Placebo groups, respectively.
  - After dose 1 and dose 2, respectively, at least one grade 3 solicited general symptom was reported for 5.8% and 10.8% of subjects in the HZ/su group; and for 3.1% and 4.0% of subjects in the Placebo group. After dose 1 and dose 2, respectively, at least one grade 3 solicited general symptom with causal relationship to vaccination as per investigator assessment was reported for 3.3% and 6.3% of subjects in the HZ/su group; and for 0.6% and 0.5% of subjects in the Placebo group.
- Regarding the duration general symptoms during the 7-day post-vaccination period, overall/dose, the median duration for fatigue and myalgia was 3.0 days for both symptoms in the HZ/su group and 5.0 and 4.0 days, respectively, in the Placebo group.

Synopsis Table 6 - Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period overall subjects and overall doses (Total Vaccinated Cohort)

		HZ/su					Placebo				
					95% CI					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/dose											
Fatigue	All	1732	751	43.4	41.0	45.7	1727	494	28.6	26.5	30.8
	Grade 3	1732	78	4.5	3.6	5.6	1727	36	2.1	1.5	2.9
	Related	1732	277	16.0	14.3	17.8	1727	96	5.6	4.5	6.7
	Grade 3 Related	1732	41	2.4	1.7	3.2	1727	7	0.4	0.2	0.8
Gastrointestinal symptoms	All	1732	292	16.9	15.1	18.7	1727	232	13.4	11.9	15.1
	Grade 3	1732	19	1.1	0.7	1.7	1727	19	1.1	0.7	1.7
	Related	1732	92	5.3	4.3	6.5	1727	35	2.0	1.4	2.8
	Grade 3 Related	1732	5	0.3	0.1	0.7	1727	1	0.1	0.0	0.3

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

		HZ/su					Placebo				
					95% CI					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Headache	All	1732	388	22.4	20.5	24.4	1727	209	12.1	10.6	13.7
	Grade 3	1732	26	1.5	1.0	2.2	1727	11	0.6	0.3	1.1
	Related	1732	146	8.4	7.2	9.8	1727	52	3.0	2.3	3.9
	Grade 3 Related	1732	15	0.9	0.5	1.4	1727	1	0.1	0.0	0.3
Myalgia	All	1732	714	41.2	38.9	43.6	1727	323	18.7	16.9	20.6
	Grade 3	1732	64	3.7	2.9	4.7	1727	20	1.2	0.7	1.8
	Related	1732	378	21.8	19.9	23.8	1727	97	5.6	4.6	6.8
	Grade 3 Related	1732	39	2.3	1.6	3.1	1727	2	0.1	0.0	0.4
Shivering	All	1732	301	17.4	15.6	19.2	1727	132	7.6	6.4	9.0
	Grade 3	1732	35	2.0	1.4	2.8	1727	7	0.4	0.2	0.8
	Related	1732	158	9.1	7.8	10.6	1727	43	2.5	1.8	3.3
	Grade 3 Related	1732	26	1.5	1.0	2.2	1727	1	0.1	0.0	0.3
Temperature/ (*) (°C)	All	1732	210	12.1	10.6	13.8	1727	56	3.2	2.5	4.2
	>39.5	1732	3	0.2	0.0	0.5	1727	1	0.1	0.0	0.3
	Related	1732	113	6.5	5.4	7.8	1727	15	0.9	0.5	1.4
	>39.5 Related	1732	3	0.2	0.0	0.5	1727	0	0.0	0.0	0.2
Overall/subject											
Fatigue	All	901	508	56.4	53.1	59.6	894	340	38.0	34.8	41.3
	Grade 3	901	66	7.3	5.7	9.2	894	31	3.5	2.4	4.9
	Related	901	210	23.3	20.6	26.2	894	79	8.8	7.1	10.9
	Grade 3 Related	901	35	3.9	2.7	5.4	894	7	0.8	0.3	1.6
Gastrointestinal symptoms	All	901	238	26.4	23.6	29.4	894	183	20.5	17.9	23.3
	Grade 3	901	18	2.0	1.2	3.1	894	17	1.9	1.1	3.0
	Related	901	79	8.8	7.0	10.8	894	30	3.4	2.3	4.8
	Grade 3 Related	901	5	0.6	0.2	1.3	894	1	0.1	0.0	0.6
Headache	All	901	302	33.5	30.4	36.7	894	166	18.6	16.1	21.3
	Grade 3	901	26	2.9	1.9	4.2	894	10	1.1	0.5	2.0
	Related	901	123	13.7	11.5	16.1	894	46	5.1	3.8	6.8
	Grade 3 Related	901	15	1.7	0.9	2.7	894	1	0.1	0.0	0.6
Myalgia	All	901	484	53.7	50.4	57.0	894	234	26.2	23.3	29.2
	Grade 3	901	56	6.2	4.7	8.0	894	19	2.1	1.3	3.3
	Related	901	279	31.0	28.0	34.1	894	83	9.3	7.5	11.4
	Grade 3 Related	901	32	3.6	2.4	5.0	894	2	0.2	0.0	0.8
Shivering	All	901	237	26.3	23.5	29.3	894	115	12.9	10.7	15.2
	Grade 3	901	35	3.9	2.7	5.4	894	7	0.8	0.3	1.6
	Related	901	131	14.5	12.3	17.0	894	38	4.3	3.0	5.8
	Grade 3 Related	901	26	2.9	1.9	4.2	894	1	0.1	0.0	0.6
Temperature/ (*) (°C)	All	901	183	20.3	17.7	23.1	894	50	5.6	4.2	7.3
	>39.5	901	3	0.3	0.1	1.0	894	1	0.1	0.0	0.6
	Related	901	101	11.2	9.2	13.5	894	15	1.7	0.9	2.8
	>39.5 Related	901	3	0.3	0.1	1.0	894	0	0.0	0.0	0.4

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
For Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
All = all subjects who have experienced the symptom
*Temperature is measured by oral, axillary, rectal or tympanic routes
Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route

Unsolicited AEs during the 30-day (Days 0-29) post-vaccination period (dose 1 and dose 2 considered):

- Overall, 360 (39.0%) subjects in the HZ/su group and 353 (38.2%) subjects in the Placebo group reported at least one unsolicited AE. Most frequent unsolicited AEs in the HZ/su group were upper respiratory tract infection (28 subjects [3.0%], reported for 30 subjects [3.2%] in the Placebo group), neutropenia (24 subjects [2.6%], reported for 25 subjects [2.7%] in the Placebo group),viral upper respiratory tract infection (23 subjects [2.5%], reported for 30 subjects [3.2%] in the Placebo group), and cough (22 subjects [2.4%], reported for 14 subjects [1.5%] in the Placebo group-. Most frequent unsolicited AEs in the Placebo group were upper respiratory tract infection, viral upper respiratory tract infection, neutropenia, cough (see incidence above) and edema peripheral (18 subjects [1.9%]; reported for 11 subjects [1.2%] in the HZ/su group).
- Overall, 60 (6.5%) subjects in the HZ/su group and 47 (5.1%) subjects in the Placebo group reported at least one grade 3 unsolicited AE. Most frequent grade 3 unsolicited symptoms in the HZ/su and Placebo groups, respectively, were neutropenia (10 subjects [1.1%] and 4 subjects [0.4%], respectively) and plasma cell myeloma (4 subjects [0.4%] and 7 subjects [0.8%], respectively). Additionally, grade 3 diarrhea was frequently reported in the Placebo group (4 subjects [0.4%], reported by 2 subjects [0.2%] in the HZ/su group).
- Overall, 31 (3.4%) subjects in the HZ/su group and 23 (2.5%) subjects in the Placebo group reported at least one unsolicited AEs with causal relationship to vaccination.
- Overall, 6 (0.7%) subjects in the HZ/su group and 5 (0.5%) subjects in the Placebo group reported at least one grade 3 unsolicited AEs with causal relationship to vaccination as per investigator assessment.
- Overall, 221 (24.0%) subjects in the HZ/su group and 192 (20.8%) subjects in the Placebo group reported at least one unsolicited AEs with medically attended visit.

SAEs, (S)AEs leading to withdrawal, pIMDs and relapse cases

Overall, there were no apparent differences in the percentage of subjects reporting SAEs, SAEs reported with causal relationship to vaccination as per investigator assessment and fatal SAEs between study groups in the different time periods evaluated. Overall, there was no cluster in the nature of the pIMDs reported and no safety concern was highlighted. No imbalance between the HZ/su and Placebo groups was observed regarding subjects withdrawn due to a non-serious AE or SAEs (data collected up Visit 5 [Month 25]).

SAEs:

- The number (%) of subjects with at least one SAE in the HZ/su group was 68 (7.4%) and 263 (28.5%) when reported from first vaccination up to 30 days post-last vaccination and up to 365 days, respectively; and in the Placebo group 66 (7.1%) and 241 (26.1%), respectively.
- The number (%) of subjects with at least one SAE with causal relationship to vaccination as per investigator assessment in the HZ/su group was 1 (0.1%) and 3 (0.3%) when reported from first vaccination up to 30 days post-last vaccination and up to 365 days post-last vaccination, respectively; and in the Placebo group 3 (0.3%) and 4 (0.4%), respectively. No additional SAEs with causal relationship to vaccination as per investigator assessment were reported in the period between 365 days post-last vaccination up to study end.

Fatal SAEs:

- The number (%) of subjects with a fatal SAE in the HZ/su group was 20 (2.2%), 77 (8.4%) and 118 (12.8%) when reported from first vaccination up to 30 days post-last vaccination, up to 365 days post-last vaccination and during the entire study period, respectively; and in the Placebo group 19 (2.1%), 79 (8.5%) and 124 (13.4%), respectively. There were no fatal SAEs reported with causal relationship to vaccination by the investigator during the entire study period.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

SAEs and AEs leading to withdrawal from study

- From first vaccination until Visit 4, there were 132 subjects withdrawn from the study due to at least one SAE (65 and 67 subjects in the HZ/su and Placebo groups, respectively). There were 28 subjects withdrawn from the study due to at least one non-serious AE (14 in each group).
- Between Visit 4 and Visit 5, there were 73 subjects withdrawn from the study due to at least one SAE (35 subjects in the HZ/su group and 38 subjects in the Placebo group). There were 12 subjects withdrawn from the study due to at least one non-serious AE (8 subjects in the HZ/su group and 4 subjects in the Placebo group).
- Between Visit 5 and the cut-off date for final analysis, there were 26 subjects in the HZ/su group and 23 subjects in the Placebo group withdrawn from the study due a fatal SAE.

pIMDs:

- The number of subjects with at least one pIMD up to 365 days post-last vaccination was 13 (1.4%) and 8 (0.9%) in the HZ/su and Placebo groups, respectively. Most frequent pIMDs (classification by PT) were psoriasis (reported for 2 [0.2%] in the HZ/su group) and interstitial lung disease (reported for 2 [0.2%] subjects in the Placebo group). All other pIMDs were reported by no more than one subject in any group.

Relapse cases:

- The number of subjects with at least one relapse case over the entire study period was 239 (25.9%) and 253 (27.4%) in the HZ/su and Placebo groups, respectively.

Pregnancies:

- A total of 14 pregnancy outcomes were reported in 11 subjects during the study period (7 subjects in the HZ/su group and 4 subjects in the Placebo group). In all cases, exposure to HZ/su / placebo occurred before pregnancy onset. From the 7 subjects in the HZ/su, there were 7 live infants with no apparent congenital anomalies and 1 elective termination.

By age strata **(**18-49 YOA and ≥ 50 YOA)

Overall, by age, there were no apparent difference in the frequency of solicited symptoms between 18-49 YOA and ≥50 YOA groups.

Safety results (unsolicited AEs, SAEs, pIMDs, relapse cases) obtained by age strata were in line with safety results reported overall. For both age strata, there were no apparent differences between HZ/su and Placebo groups.

Important safety information received after the data lock point (database freeze date):
No important additional safety information was available after the data lock point.

Conclusion:

Except for the analyses of the primary endpoint, all the other analyses (of secondary and tertiary endpoints including by subgroup analyses) were exploratory. The study was not designed to draw confirmatory conclusions on these analyses as no control of type I error was done.

Efficacy

The overall HZ VE in autologous HCT recipients ≥ 18 YOA (mTVC) was 68.17% (95% CI: 55.56% - 77.53%; P<0.0001) after an approximate median follow-up time of 21 months (approximately 22 months in the HZ/su group and approximately 20 months in the Placebo group). The primary objective of the study was met as statistically significant VE (68.17%, p<0.0001) was demonstrated in the prevention of HZ in autologous HCT recipients ≥ 18 YOA with a LL of the 95% CI (55.56%) above 0%.

Results from secondary objectives suggest that HZ/su can prevent PHN and HZ-related complications in autologous HCT recipients ≥ 18 YOA, and can reduce the duration of severe 'worst HZ associated pain' in subjects of this population with confirmed HZ.

Results from tertiary objectives suggest also an effect of HZ/su against HZ during 1 year post-HCT and an effect against HZ–related hospitalizations in autologous HCT recipients ≥ 18 YOA.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Quality of Life

Consistent differences were observed in favor of the HZ/su group compared to the Placebo group when measuring pain associated with the HZ episode using the ZBPI worst and average pain scores, the derived ZBPI time to resolution of clinically significant pain, and Burden of illness/Burden of interference scores, suggesting that the severity of disease was reduced in the HZ/su group compared with the Placebo group.

Immunogenicity

In autologous HCT recipients ≥ 18 YOA, HZ/su elicited strong anti-gE Ab responses and gE-specific CMI responses following 2 doses of HZ/su at one month post-dose 2 (Month 2) that persisted up to two years post-dose 2 (Month 25) relative to pre-vaccination levels.

Safety

In autologous HCT recipients ≥ 18 YOA, HZ/su was shown to have a clinically acceptable profile. No safety concern was identified.

Overall, a higher percentage of subjects reported solicited local and general AEs (any grade, grade 3, related and grade 3 related as per investigator assessment) during the 7-day post-vaccination period in the HZ/su group compared to the Placebo group. In the HZ/su group, the most frequently reported solicited local symptom observed was pain, and the most frequently reported solicited general symptoms were fatigue and myalgia.

Overall, there were no apparent differences between HZ/su and Placebo groups for unsolicited AEs during the 30-day post-vaccination period.

There were no apparent differences between HZ/su and Placebo groups in the percentage of subjects with SAEs, SAEs reported with causal relationship to vaccination as per investigator assessment, or fatal SAEs reported during the study.

No fatal SAE with causal relationship to vaccination (as per investigator assessment) was reported in the study.

There was no cluster in the nature of the pIMDs reported and no safety concern was identified.

There were no apparent differences between HZ/su and Placebo groups in the percentage of subjects with relapse cases reported during the study.

There was no apparent imbalance between the HZ/su and the Placebo groups regarding subjects withdrawn from the study due to SAEs or AEs.

References:

Miettinen OS, Nurminen M. Comparative analysis of two rates. *Stat Med.* 1985; 4: 213-226.

Date of Report: Final: 22 February 2018

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Study No.: 115523 (ZOSTER-002)

Title of the study:

A phase III, randomized, observer-blind, placebo-controlled, multicentre, clinical trial to assess the prophylactic efficacy, safety, and immunogenicity of GSK Biologicals' herpes zoster gE/AS01$_B$ candidate vaccine when administered intramuscularly on a two-dose schedule to adult autologous haematopoietic stem cell transplant (HCT) recipients.

This report provides all final vaccine efficacy (VE) data from the ZOSTER-002-analyses, including Quality of Life (QoL) data, and reactogenicity/safety data ***(including specific safety analyses requested by the Center for Biologics Evaluation and Research [CBER])*** *as well as humoral and cell-mediated immunogenicity data, obtained for HZ/su, previously referred to as gE/AS01$_B$. Correlate of protection (CoP) analysis will be presented in a future report.* ***(Amended 02 May 2019)***

Investigators and study centers:

Multicenter study conducted in 28 countries: Australia, Belgium, Bulgaria, Canada, Czech Republic (Czechia), Estonia, Finland, France, Germany, Greece, Hong-Kong, Israel, Italy, Japan, Malaysia, the Netherlands, New Zealand, Panama, Poland, Romania, Republic of Korea, Russian Federation, South Africa, Spain, Taiwan, Turkey, United Kingdom and United States (US).

The following Principal Investigators involved in this study reviewed the Clinical Study Report (CSR): Dr. Gaidano, SCDU (Struttura Complessa a Direzione Universitaria) di Ematologia, Azienda Ospedaliera Universitaria Maggiore di Novara, Italy; Dr. de la Serna, Hospital Universitario 12 de Octubre, Madrid, Spain; Dr. Quittet, Centre Hospitalier Régional Universitaire de Montpellier - Hôpital Saint Eloi, France; Dr. Issa, Massachusetts General Hospital and Division of Infectious Diseases, Brigham and Women's Hospital, Boston, Massachusetts, US; Dr. Chou, Niigata Cancer Center Hospital, Niigata, Japan.

Publication (reference): None at the time of this report.

Study period: **Study initiation date:** 13 July 2012 **Study completion date:** 01 February 2017 **Data lock point (Date of database freeze):** 05 September 2017	**Phase:** III

Indications: Prevention of HZ and related complications in adults ≥ 50 years of age (YOA) and immunocompromised adults ≥ 18 YOA.

Objectives:

Primary:

- To evaluate VE in the prevention of HZ in autologous HCT recipients 18 YOA and older.

  Criterion used: Clinically meaningful overall HZ VE was demonstrated if the lower limit (LL) of the 95% confidence interval (CI) was above 0%.

Secondary:

- To evaluate VE in reducing the total duration of 'worst' HZ-associated pain over the entire pain reporting period in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in the reduction of confirmed HZ-associated complications in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the prevention of post-herpetic neuralgia (PHN) in autologous HCT recipients 18 YOA and older;
- To evaluate humoral immune responses to the study vaccine, when administered according to a 2-dose schedule in a sub-cohort of subjects;
- To evaluate vaccine safety and reactogenicity in autologous HCT recipients 18 YOA and older.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Tertiary:

- To evaluate VE in the prevention of HZ in autologous HCT recipients 18 YOA and older when all subjects reach 1 year post-HCT;
- To evaluate VE in the prevention of PHN in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in reducing the severity of acute HZ-associated pain in HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in improving QoL in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate VE in the reduction of overall mortality in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the reduction of HZ-related mortality in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the reduction of overall hospitalizations in autologous HCT recipients 18 YOA and older*;
- To evaluate VE in the reduction of HZ-related hospitalizations in autologous HCT recipients 18 YOA and older;
- To evaluate VE in the reduction in duration of pain medications in autologous HCT recipients 18 YOA and older with confirmed HZ;
- To evaluate cell-mediated immune response to the study vaccine in a sub-cohort of subjects;
- To assess correlation of vaccine-induced humoral immune responses with protection against HZ**.

*This assessment was not performed but descriptive safety tables and serious adverse event (SAE) listings were provided.

**Data regarding CoP assessment are planned to be presented in a future report.

Methodology:

This was a phase III, observer-blind randomized, placebo-controlled, multi-center, multi-country study with two parallel groups to evaluate the efficacy of HZ/su, when administered intramuscularly on a 0 and 1 to 2 months schedule, in the prevention of HZ in autologous HCT recipients 18 YOA and older.

The first vaccination visit at Month 0 (Visit 1) was preceded by a Pre-vaccination visit that took place from 110 days prior to Visit 1 up to the day of Visit 1 (the Pre-vaccination visit could occur on the same day as Visit 1).

Eligible subjects were randomized to HZ/su or placebo according to a 1:1 ratio (*HZ/su was previously referred to as gE/AS01$_B$*).

The randomization algorithm used a minimization procedure accounting for different factors: age (18-49 YOA and ≥ 50 YOA), underlying-disease characteristics (subjects with an underlying diagnosis of multiple myeloma and all other diagnoses for which the HCT was undertaken), post-transplant antineoplastic therapy (subjects undergoing antineoplastic maintenance therapy with bortezomib at the time of first vaccination and subjects not undergoing antineoplastic maintenance therapy with bortezomib at the time of first vaccination, even if receiving another antineoplastic therapy), anticipated duration of post-transplant antiviral prophylaxis (duration of post-transplant antiviral prophylaxis up to and including 3 months [including subjects who as per standard of care did not receive any antiviral prophylactic therapy] and duration of post-transplant antiviral prophylaxis from more than 3 months up to and including 6 months), center, and gender. Overall, target enrolment was approximately 1063 subjects receiving HZ/su and approximately 1063 subjects receiving a placebo.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)
For female subjects of childbearing potential, a urine pregnancy test was performed at Visit 1 (Month 0) and Visit 2 (Month 1, i.e., 1 to 2 months after Visit 1). A serum pregnancy test at Visit 1 or Visit 2 was performed if required per local or ethics committee regulation.		

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Study staff provided subjects a diary card after each vaccination for daily recording of solicited ***adverse events (AEs)*** (Days 0 to 6) and unsolicited ***AEs*** (Days 0 to 29). ***(Amended 02 May 2019)***

SAEs and potential immune-mediated diseases (pIMDs) were collected and recorded from the first receipt of study vaccine/placebo up to Visit 4 (Month 13). Fatal SAEs were collected and recorded from the Pre-vaccination visit until study end. SAEs that were related to the investigational product were collected and recorded from the time of the first receipt of study vaccine/placebo (Visit 1, Month 0) until study end. Any relapse, i.e., a recurrence of the underlying malignancy or disease for which the HCT was undertaken, was to be recorded, from Visit 1 (Month 0) until study end. Pregnancies were to be reported from Month 0 until study end.

Blood samples were collected from all subjects at Visits 1 (pre-vaccination, Month 0) and 3 (post-second vaccination, Month 2) to possibly contribute to the CoP assessment.

Additionally, blood samples were collected from a subset of subjects (the Humoral Immunogenicity sub-cohort) at post-first vaccination at Visit 2 (Month 1), and post-second vaccination at Visit 4 (Month 13) and Visit 5 (Month 25) to assess persistence of humoral immune response. In these subjects, blood samples were also collected at Visit 1 and 3 to assess for humoral immune response.

Blood samples were collected from a sub-cohort of subjects (i.e., the cell-mediated Immunogenicity [CMI]-sub-cohort) at Visits 1, 2, 3, 4 and 5 to assess CMI responses. The CMI sub-cohort was a subgroup of the Humoral Immunogenicity sub-cohort.

After Visit 3, monthly contacts between the subjects and the investigator and/or his delegate took place to collect information on any event of interest that might have occurred. The contacts were not to take place at months that coincided with the subject's scheduled study visits (i.e., Visit 4 and 5).

In case of a suspected HZ episode, the subject had to complete a HZ-specific diary card and questionnaires and had additional visits and contacts for follow-up of HZ.

Whenever possible, rash lesion samples were collected from subjects clinically diagnosed as having a suspected case of HZ with characteristic HZ or VZV rash (HZ according criterion 1). A suspected case of HZ could be confirmed by polymerase chain reaction (PCR), or by the HZ Ascertainment Committee (HZAC, referred to as HZ Adjudication Committee in the HZAC charter, version 1, dated 04 October 2012, on file at GSK Biologicals). All suspected HZ cases were referred to the HZAC in a blinded manner. The HZAC classified these cases as either "HZ", "not HZ" or "not able to decide" (note that the protocol did not specify the "not able to decide" category). However, the HZAC classification served as the final case definition only when the case could not be confirmed or excluded by PCR; e.g., when all samples from a given subject were inadequate (as when both VZV and β-actin PCR results were negative), or when no samples were available for a given subject. Therefore, definitive PCR results, when available, determined the final HZ case assignment. If the case could not be confirmed or excluded by PCR and the HZAC final outcome was 'not able to decide', the overall final outcome was 'No possible classification'; for analysis the categories 'not HZ' and 'No possible classification' were considered as 'not HZ'. PCR test results or HZAC classification as described above would not have served as the final case definition if the following applied: cases of suspected HZ were not considered a confirmed case of HZ for the efficacy analysis if they potentially could constitute a primary VZV infection.

Cases of HZ with characteristic VZV or HZ rash and PHN associated with a case of HZ were to be recorded from Month 0 until study conclusion in HZ-specific screens. Any pre-defined HZ complication (different from PHN) was to be recorded, from Month 0 until study end, on an SAE or AE screen as appropriate. Cases of HZ without characteristics VZV or HZ rash (HZ according criterion 2) were to be recorded from Month 0 until study end on an SAE screen, and were to be specified there as related to HZ.

Zoster Brief Pain Inventory (ZBPI) questionnaires were completed to assess HZ-associated pain (broadly defined to include allodynia, pruritus or other sensations) and discomfort during an HZ episode and the impact of HZ on subject's QoL. PHN cases identified based on ZBPI reporting were considered for statistical analyses.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

QoL questionnaires Euro-QoL 5 Dimension (EQ-5D) and Short form-36 (SF-36) were completed by all subjects at Visits 1, 3 and 4 and in case of suspected HZ.

An Independent Data Monitoring Committee (IDMC) was appointed to monitor and follow-up the safety and tolerability of HZ/su. Unblinded evaluation of the safety data (with coded group names) was performed by the IDMC on an ongoing basis. The IDMC met periodically during the trial to review safety data and make recommendations regarding continuation, modification or discontinuation of the study following each meeting. The IDMC concluded after each review that the trial could continue as planned.

Study end was triggered on 04 November 2016 when the conditions for final triggered analysis were met (i.e., there were at least 125 confirmed HZ cases in the primary cohort for efficacy and all subjects had completed Visit 4 [Month 13]). Data contributing to the analysis of the primary efficacy objective (HZ cases) were collected until the cut-off date (04 November 2016). Conclusion visits took place after the cut-off date for final triggered analysis. Between the cut-off date and conclusion visits, safety data continued to be collected until study conclusion. In addition, each suspected HZ case ongoing at the time of the cut-off date for final triggered analysis, was followed for at least 90 days to allow accurate diagnosis of PHN. Study end (last subject last visit) occurred on 01 February 2017. All data (except the data regarding CoP assessment) accrued up to study end were included in the analysis and are presented in the study report.

Study vaccine and comparator, dose, mode of administration, lot no.:

Vaccination schedule/site:

HZ/su group subjects received 2 doses of HZ/su.

Placebo group subjects received 2 doses of placebo.

For both groups, the first dose was administered at Visit 1 and the second dose at Visit 2 (1 to 2 months after the first dose) through intramuscular injection into the deltoid muscle of the non-dominant arm. In rare situations when there was no alternative, the injection could be given in the other arm.

Study vaccine and comparator composition/dose/lot number:

Treatment name	Product name*	Formulation	Presentation	Volume to be administered	Lot numbers
HZ/su	VZV gE	50 μg gE per 0.5 mL of reconstituted vaccine	Lyophilized pellet in a monodose vial	0.5 mL	DVZVA007A, DVZVA008A, DVZVA007B
	$AS01_{B}$*	MPL, QS21 and liposome (50 μg MPL and 50 μg QS21) per 0.5 mL of reconstituted vaccine	Liquid in a monodose vial		DA01A052A, DA01A055A, DA01A050A
Placebo	Lyophilized sucrose cake	20 mg sucrose per 0.5 mL of reconstituted placebo	Lyophilized pellet in a monodose vial	0.5 mL	PVZVA003A, PVZVA005A
	Saline (NaCl) solution for reconstitution	150 mM NaCl solution (water for injection)	Liquid in a monodose vial		DD02A009, DD02A011A

HZ/su = Herpes Zoster subunit vaccine; VZV = Varicella Zoster Virus; gE = recombinant purified Glycoprotein E; $AS01_{B}$ = Adjuvant System $AS01_{B}$; NaCl = Sodium Chloride; MPL = 3-O-desacyl-4'-monophosphoryl lipid A; QS21 = *Quillaja saponaria* Molina, fraction 21 (Licensed by GSK from Antigenics Inc., a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)
*Components of the reconstituted study vaccine HZ/su (referred in the protocol to as gE/$AS01_{B}$) and placebo, respectively.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Study Population:

Male and female subjects at least 18 years old (and having reached the age of local legal consent) at the time of study entry, who had provided informed consent, had undergone or were to undergo autologous HCT within 50-70 days prior to the first vaccination with the study vaccine/placebo, and with, at study entry, no planned additional HCTs (tandem autologous HCT recipients could participate following their final HCT).

Female subjects were to be of non-childbearing potential or were to practice adequate contraception for a minimum of 30 days prior to vaccination to be continued through 12 months post-study vaccinations and to have a negative pregnancy test before each vaccination dose.

Subjects receiving prophylactic antiviral therapy (with activity against VZV) expected to last more than 6 months after transplantation were excluded. Subjects having a varicella or HZ episode by clinical history or a varicella or HZ vaccination within the 12 months preceding the first study vaccination were excluded, as well as subjects who had planned to receive during the study a HZ vaccine (including an investigational or non-registered vaccine) other than the study vaccine.

Duration of treatment:

The exact study duration varied between subjects. Each subject was to be followed at least until he/she completed Visit 4 (i.e., until Month 13), approximately 12 months after the second dose of study vaccine/placebo, and there were at least 125 confirmed HZ cases in the primary cohort for efficacy (cut-off date final triggered analysis: 04 November 2016).

Once conditions for final triggered analysis were met, the conclusion visit was to take place. Any remaining monthly contacts after Visit 4, Visit 5, and monthly contacts after Visit 5 were not to take place. Each suspected HZ case ongoing at the cut-off date for final triggered analysis was to be followed for at least 90 days. The maximal study duration recorded in the study for a subject was approximately 4 years.

Criteria for evaluations:

Primary endpoint:

- Occurrence of confirmed HZ cases
  - Incidence of confirmed HZ cases from Month 0 until study end.

Secondary endpoints:

- Duration of 'worst' HZ-associated pain
  - Duration of HZ-associated pain rated as 3 or greater on the 'worst pain' ZBPI question, following the onset of a confirmed HZ rash over the entire pain reporting period in subjects with confirmed HZ;
- Occurrence of confirmed HZ-associated complications
  - Incidence of confirmed HZ complications following the onset of HZ from Month 0 until study end;
- Occurrence of PHN
  - Incidence of PHN from Month 0 until study end;
- Antigen-specific antibody (Ab) concentrations in a sub-cohort of subjects
  - Anti- gE Ab concentrations as determined by ELISA in a sub-cohort of subjects at Month 0, Month 1, Month 2, Month 13 and Month 25;
- Occurrence of solicited local and general ***AEs***
  - Occurrence and intensity of each solicited local ***AE*** within 7 days (Days 0-6) after each vaccination in all subjects;
  - Occurrence, intensity and relationship to vaccination of each solicited general ***AE*** within 7 days (Days 0-6) after each vaccination, in all subjects; ***(Amended 02 May 2019)***

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

- Occurrence of unsolicited AEs
  - 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;
- Occurrence of SAEs
  - Occurrence and relationship to vaccination of all SAEs from Month 0 until Month 13 in all subjects;
  - Occurrence of SAEs related to the GSK study vaccine/placebo from Month 0 until study end in all subjects;
  - Occurrence of SAEs related to study participation or to a concurrent GSK medication/vaccine from the Pre-vaccination visit until study end in all subjects;
  - Occurrence of any fatal SAEs from the Pre-vaccination visit until study end in all subjects;
- Occurrence of AEs of specific interest
  - Occurrence and relationship to vaccination of any pIMD from Month 0 until Month 13 in all subjects;
  - Occurrence of relapse cases from Month 0 until study end in all subjects.

  Relapse: recurrence of the underlying malignancy or disease for which the HCT was undertaken.

Tertiary endpoints:

- Occurrence of confirmed HZ cases in subjects having at least 1 year post-HCT
  - Incidence of confirmed HZ cases in subjects having at least 1 year post-HCT;
- Occurrence of PHN in subjects with confirmed HZ
  - Incidence of PHN from Month 0 until study end in subjects with confirmed HZ;
- Acute HZ severity
  - Acute HZ severity as determined by the mean Area Under Curve (AUC) of the severity-by-duration of HZ-associated pain as measured by the ZBPI during a 4-week period following the onset of confirmed HZ in subjects with confirmed HZ;
- Interference of HZ with QoL
  - Interference of HZ with QoL as measured by ZBPI in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by EQ-5D in subjects with confirmed HZ;
  - Interference of HZ with QoL as measured by SF-36 in subjects with confirmed HZ;
- Occurrence of overall mortality
  - Incidence of overall mortality from Month 0 until study end;
- Occurrence of HZ-related mortality
  - Incidence of HZ-related mortality from Month 0 until study end;
- Occurrence of overall hospitalizations*
  - Incidence of overall hospitalizations from Month 0 until study end;
- Occurrence of HZ-related hospitalizations
  - Incidence of HZ-related hospitalizations from Month 0 until study end;
- Duration of pain medication administered for HZ
  - Duration of pain medication administered for HZ from Month 0 until study end in subjects with confirmed HZ;
- CMI in terms of frequencies of antigen-specific CD4+ T-cells in a sub-cohort of subjects
  - Frequencies of CD4+ T-cells following induction with gE antigens, as determined by *in vitro* intracellular cytokine staining (ICS), expressing at least 2 activation markers (from

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among IFN-γ, IL-2, TNF-α and CD40L**) in a sub-cohort of subjects at Month 0, Month 1, Month 2, Month 13 and Month 25;

- Frequencies of CD4+ T-cells following induction with gE antigens, as determined by *in vitro* ICS, expressing each individual activation marker in addition to one other marker (from among IFN-γ, IL-2, TNF-α and CD40L) in a sub-cohort of subjects at Month 0, Month 1, Month 2, Month 13 and Month 25;

- Antigen-specific Ab concentrations at Month 0 and at Month 2 in subjects with confirmed HZ***
  - Anti-gE Ab concentrations as determined by enzyme-linked immunosorbent assay (ELISA) at Month 0 and at Month 2, in all subjects with confirmed HZ compared to matched controls.

*This analysis was not performed but descriptive safety tables and SAE listings were provided.

**IFN-γ = interferon gamma; IL-2 = Interleukin-2; TNF-α = Tumor Necrosis Factor alpha; CD40L = CD40 Ligand

***Data regarding CoP assessment will be presented in a future report.

Statistical methods:

- Analysis of demographics and other baseline characteristics

Demographic characteristics (age at first study vaccination, gender, geographic ancestry and ethnicity) were tabulated overall.

The cohorts description and withdrawal status from the study were summarized using descriptive statistics.

- Analysis of efficacy

The primary efficacy analysis was based on the modified Total Vaccinated Cohort (mTVC), which excluded subjects in the Total Vaccinated Cohort (TVC) analysis who were not administered with the second vaccination or who received vaccine doses /or replacement not on the same group or who developed a confirmed case of HZ prior to 1 month after the second vaccination.

Reduction in HZ risk

The primary analysis method of the VE considered the exact inference on the relative risk conditionally to the total number of HZ cases observed and time at risk.

This method computes an exact CI around the rate ratio (ratio of the event rates in the vaccinated versus control group) and takes into account the sum of the time at risk of the subjects within each group.

Relative risk (RR) was defined as the ratio of the incidence rates of the HZ/su group over the Placebo group. VE = 1 – RR.

The time at risk for a subject was calculated from HZ onset to time zero relative to the cohort considered: from first vaccination for TVC and from 30 days following the second vaccination for mTVC and According to Protocol (ATP) cohort for efficacy. The number of Person-Years at risk was defined as the sum of the time at risk for all subjects at risk during, either up to the cut-off date for the analysis (04 November 2016), the censoring date (drop-out;) or the occurrence of the first HZ case for a subject.

In addition, subjects with relapse of the original malignancy or disease for which the HCT was undertaken were censored from the mTVC and ATP analysis from the date that they started the therapy to treat relapse.

Reduction in overall PHN and HZ associated complications risks

The overall reduction in PHN risk was evaluated similarly to the HZ risk using the exact inference on the RR conditionally to the total number of PHN cases observed and time at risk. PHN was defined by the presence of HZ-associated severe “worst” pain persisting or appearing more than 90 days after

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onset of the HZ rash. For this analysis, severe "worst" pain was defined as HZ-associated pain rated as 3 or greater on the "worst pain" ZBPI question.

The same approach was used to analyses the reduction in the risk of HZ-associated complications.

Reduction in PHN incidence in subjects with an HZ episode

The incidence of PHN, in subjects with an HZ episode, was presented and compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985].

Reduction of duration of 'worst' pain in subjects with an HZ episode and duration of pain medications

The analysis of duration of 'Worst pain' involved any subject reporting ZBPI pain scores of 3 or more at any time during the study. The time-to-cessation of severe 'worst' pain was analyzed using a survival methodology. Cox -proportional model was used to assess the hazard rate reduction in ZBPI worst pain duration due to the vaccine in those subjects that presented HZ. The same approach was used to analyze the reduction in the duration of pain medications.

The use of pain medication, in subjects with an HZ episode was compared with placebo using asymptotic standardized unconditional binomial test [Miettinen, 1985].

Reduction in overall mortality and HZ-associated mortality and hospitalization

The analysis of (overall and HZ associated) mortality was based using Cox's proportional hazard regression using age group, underlying diseases and the anticipated duration of post-transplant antiviral prophylaxis factors with vaccine groups as covariates. VE was then calculated as 1 minus the hazard ratio. A similar approach was used for the analysis of HZ-related hospitalizations.

- Analysis of Quality of Life

Analysis of Quality of Life by ZBPI

The severity of HZ-Pain was measured from the ZBPI worst pain score at Days 30, 90 and 182 using AUC methods. The mean pain was compared across vaccine groups using the non-parametric Wilcoxon test. Time to resolution of clinically significant pain was analyzed for the HZ ZBPI evaluable subgroup. An event was defined as having a worst pain score < 3 for a documented 4-week clinically significant pain-free period. Time-to-event curves were estimated using the Kaplan-Meier method. A log rank test was used to compare vaccine groups.

The HZ severity-of-illness score and HZ burden-of-illness scores were calculated from the ZBPI worst pain scores and the HZ severity-of-interference score and HZ burden-of-interference score were calculated from the ZBPI Activities of Daily Living (ADL) score, over the 182 days from the first day of HZ rash (HZR Day0) using AUC methods. The burden and severity scores were calculated based on the mTVC. The scores were defined as 0 for participants who did not develop an evaluable case of HZ during the study. Subjects who had a confirmed HZ episode but did not complete any ZBPI assessments were considered missing for this analysis.

Analysis of Quality of Life using SF-36 and EQ-5D

Data for HZ cases were analyzed using (a) descriptive statistics, (b) repeated measures analysis of variance and (c) a multivariate Rank Analysis of repeated measures ordinal categorical for the multi-item SF-36 and EQ-5D scales for each vaccine group.

Estimation of HZ impact on utility score: A model was fitted to estimate the HZ impact on both the EQ-5D and SF-36 utility scores in the Placebo group only stratified by age. The model included the baseline utility scores, i.e., most recent pre-HZ assessment (at one of Months 0, 2 or 13) and the utility scores during the first four weeks of the HZ episode.

- Analysis of humoral immunogenicity

The primary analysis was based on the ATP cohort for analysis of humoral immunogenicity which included all evaluable subjects planned in the humoral immunogenicity sub-cohort and meeting protocol requirements for the inclusion in the ATP cohort for humoral immunogenicity.

The analysis method of the post-vaccination log-transformed immunogenicity marker data at Month 2 used a likelihood-based model with repeated measurements (including Month 1 and Month 2). The

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fixed-effect model included the means for two levels of the treatment effect and adjusted for age strata and underlying diseases. The pre-vaccination log-transformed values were included as continuous covariate. For each group, adjusted means and difference of means between treatment groups were calculated together with 95% CIs (2-sided) and back-transformed to the original units to provide geometric means (GMs) and GM ratios.

- Analysis of CMI

The primary analysis was based on the ATP cohort for analysis of CMI which included all evaluable subjects planned in the CMI sub-cohort and meeting protocol requirements for the inclusion in the ATP cohort for CMI. The primary evaluation of the vaccine on CMI endpoint was based on treatment group comparison in the frequency of gE-specific CD4+ T-cell secreting at least 2 activation markers among IL-2, IFN-γ, TNF-α, and CD40L (i.e., CD4 [2+] T-cell frequency). A likelihood-based Analysis of Covariance (ANCOVA) model with repeated measurement (including Month 1 and Month 2) was used to analyze the log-transformed ratio between induction frequency and background frequency of CD4[2+]. The fixed-effect model included the means for two levels of the treatment group effect. The age strata and underlying diseases were included in the model.

The continuous covariates included: the pre-vaccination log-transformed CD4[2+] T-cell frequency following induction with gE and the post-vaccination log-transformed CD4+ T-cell frequency under background condition. Least-square means and difference of least-squares means were then back-transformed and used to provide estimates for the frequency difference divided by background ([induction – background] / background). Primary timepoint is Month 2.

- Analysis of safety

The primary analysis was based on the TVC which included all vaccinated subjects with respect to the vaccine actually administered. ***Unless otherwise specified, the analyses of AEs included both non-serious and serious AEs.*** The percentage of subjects reporting each solicited local and general AE during the solicited 7-day-follow-up period was tabulated with exact 95% CI. The same tabulation was performed for grade 1 and above, grade 2 and above and grade 3 solicited AEs and for solicited general AEs with relationship to vaccination. The proportion of subjects with at least one report of unsolicited AE ***(all unsolicited AEs / unsolicited AEs with relationship to vaccination / grade 3 unsolicited AEs / grade 3 unsolicited AEs with relationship to vaccination / grade 3 non-serious unsolicited AEs [additional specific safety analysis] / grade 3 non-serious unsolicited AEs with relationship to vaccination [additional specific safety analysis] and unsolicited AEs with medically attended visit)*** classified by the MedDRA Preferred Terms ***(PTs)*** and reported up to 30 days after each vaccination was tabulated with exact 95% CI. SAEs and pIMDs reported up to 365 days post-last vaccination were tabulated. Withdrawals due to (S)AEs up to Visit 5 were tabulated, and withdrawals due to fatal SAEs from after Visit 5 up to cut-off date. Fatal SAEs, SAEs considered related as per investigator assessment and relapses from first vaccination up to study end were tabulated. ***Number and percentage of subjects who died were tabulated by the date of death (additional specific safety analysis) and the onset date of the fatal SAE, classified by MedDRA System Organ Class (SOC) and PT. (Amended 02 May 2019)***

Synopsis Table 1: Study population (Total vaccinated cohort)

Number of subjects	**HZ/su**	**Placebo**
Planned, N	1063	1063
Randomised, N (Total Vaccinated Cohort)	922	924
Completed, n (%)	694 (75.3)	672 (72.7)
Demographics	**HZ/su**	**Placebo**
N (Total Vaccinated Cohort)	922	924
Females:Males	342:580	346:578
Mean Age, years (SD)	54.8 (11.7)	55.1 (11.4)
Median Age, years (minimum, maximum)	57 (18, 78)	58 (18, 75)
White - Caucasian / European Heritage, n (%)	715 (77.5)	712 (77.1)
Asian - East Asian Heritage, n (%)	83 (9.0)	91 (9.8)

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Asian - Japanese Heritage, n (%)	43 (4.7)	38 (4.1)

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
Completed = until 04 November 2016 (subjects with a study conclusion date on or after the cut-off date for final analysis [04 November 2016])
Note: The 3 most frequent geographic ancestries are presented in the table. Geographic ancestries occurring less frequently (< 4.1% of subjects in the HZ/su and Placebo groups, respectively) were the following: African Heritage / African American, American Indian or Alaskan Native, Asian - Central/South Asian Heritage, Asian - South East Asian Heritage, White - Arabic / North African Heritage, Other.
Of note between the cut-off date for final analysis (4 November 2016) until study conclusion, 6 subjects (3 in each group) incurred a fatal outcome.

Summary:

Except for the analyses of the primary endpoint, all the other analyses (of secondary and tertiary endpoints including by subgroup analyses) were exploratory. The study was not designed to draw confirmatory conclusions on these analyses as no control of type I error was done.

Efficacy results:

Primary objective:

HZ VE in autologous HCT recipients ≥ 18 YOA (mTVC)

In the primary HZ VE (first or only episode of HZ) analysis on mTVC, a total of 184 subjects reported at least one confirmed HZ episode, amongst which 49 were in the HZ/su group and 135 in the Placebo group. All confirmed HZ episodes were cases of HZ with characteristic VZV or HZ rash (HZ according criterion 1). The median follow-up time was approximately 21 months; with approximately 22 months in the HZ/su group and approximately 20 months in the Placebo group.

The overall HZ VE (first or only episode of HZ) was 68.17% (95% CI: 55.56% - 77.53%; P<0.0001). The primary objective of the study was met since the LL of the 95% CI was above 0% (see Synopsis Table 2).

Subgroup analyses of HZ VE:

- HZ VE by age strata:
  - 18-49 YOA: 71.77% (95% CI: 38.75% - 88.25%)
  - ≥ 50 YOA: 67.34% (95% CI: 52.60% - 77.89%)
- HZ VE by underlying diseases:
  - Multiple myeloma: 72.35% (95% CI: 54.76% - 83.71%)
  - Other diagnoses: 63.63% (95% CI: 42.29% - 77.66%)
- HZ VE by gender:
  - Female: 77.60% (95% CI: 60.66% - 87.95%)
  - Male: 60.28% (95% CI: 39.37% - 74.48%)

Note:

The results obtained on the TVC and ATP cohort for efficacy were in line with results obtained on the mTVC.

Synopsis Table 2: Vaccine efficacy: First or only episode of HZ during the entire study period using Poisson method (modified Total Vaccinated Cohort)

									VE			
	HZ/su				**Placebo**					**95% CI**		
Type	**N**	**N**	**T (year)**	**n/T (per 1000)**	**N**	**n**	**T (year)**	**n/T (per 1000)**	**(%)**	**LL**	**UL**	**p-value**
OVERALL	870	49	1633.1	30.0	851	135	1431.9	94.3	68.17	55.56	77.53	<0.0001

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group

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N = number of subjects included in each group
N = number of subjects having at least one confirmed HZ episode
T (year) = sum of follow-up period (censored at the first occurrence of a confirmed HZ episode and at the occurrence of treatment for relapse) expressed in years
n/T (per 1000) = Incidence rate of subjects reporting at least one event
LL, UL = 95% Lower and Upper confidence limits
VE (%) = Vaccine Efficacy (Poisson method)
P-value = Two sided Exact P-value conditional to number of cases

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Secondary objectives

Reduction of duration of severe 'worst' HZ associated pain in autologous HCT recipients ≥ 18 YOA with a confirmed HZ episode (mTVC):

The VE in subjects with a confirmed HZ episode in terms of reduction of duration of severe 'worst' HZ-associated pain was 38.53% (95% CI: 11.05% - 57.52%).

VE against HZ related complications in autologous HCT recipients ≥ 18 YOA (mTVC)

At least one HZ complication was observed in 3 out of 870 subjects of the HZ/su group and 13 out of 851 subjects of the Placebo group. Reported HZ complications were HZ meningoencephalitis (1 subject in the Placebo group) and HZ cutaneous disseminated (3 subjects in the HZ/su group and 12 subjects in the Placebo group).

The overall VE against HZ related complications during the entire study period was 77.76% (95% CI: 19.05% - 95.93%).

VE in the prevention of overall PHN in autologous HCT recipients ≥ 18 YOA (mTVC)

There were 10 subjects with PHN episodes, 1 was in the HZ/su group and 9 were in the Placebo group.

The overall PHN VE (first or only episode of PHN) during the entire study period was 89.27% (95% CI: 22.54% - 99.76%).

Tertiary objectives

HZ VE during 1 year post-HCT in autologous HCT recipients ≥ 18 YOA (mTVC)

The HZ VE during 1 year post-HCT (median follow-up time was 7.6 months, with 7.7 months in the HZ/su group and 7.6 months in the Placebo group) was76.15% (95% CI: 61.11% - 85.98%).

Reduction of PHN incidence in autologous HCT recipients ≥ 18 YOA with a confirmed HZ episode (mTVC)

In subjects with a confirmed HZ episode, PHN was reported in 1 out of 49 subjects of the HZ/su group and 9 out of 135 subjects of the Placebo group.

The VE in terms of reduction of PHN incidence in subjects with a confirmed HZ episode was 69.39% (95% CI: -77.38% - 94.97%).

Reduction of overall and confirmed HZ episode related mortality and confirmed HZ episode related hospitalizations in autologous HCT recipients ≥ 18 YOA (mTVC)

HZ-related mortality was not observed in the autologous HCT recipients ≥ 18 YOA.

HZ-related hospitalizations were observed in 2 subjects of the HZ/su group and 13 subjects of the Placebo group.

The VE against first or only episode of confirmed HZ episode related hospitalizations during the entire study period was 84.70% (95% CI: 32.15% - 96.55%).

Reduction in use and duration of HZ-associated pain medications in autologous HCT recipients ≥ 18 YOA with a confirmed HZ episode (mTVC)

In subjects with a confirmed HZ episode, 32 (65.31%) out of 49 subjects and 94 (69.63%) out of 135 subjects in the HZ/su group and the Placebo group, respectively, took at least one pain medication associated with HZ during the entire study period.

The VE in terms of reduction in use of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode was 6.21% (95% CI: -15.84% - 27.82%).

The VE in terms of reduction in duration of pain medication associated with HZ during the entire study period in subjects with a confirmed HZ episode was 22.45% (95% CI: -15.85% - 48.09%).

Quality of Life results:

A summary of the results of the QoL analyses is presented:

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- Consistent differences were observed in favor of the HZ/su group compared to the Placebo group when measuring pain associated with the HZ episode using the ZBPI.
- The overall VE estimate for the ZBPI burden-of-illness score was 82.5% (95% CI: 73.6% - 91.4%). The overall VE estimate for the ZBPI burden-of-interference score was 82.8% (95% CI: 73.3% - 92.3%).
- The median time to resolution of clinically significant pain was 20 days in the HZ/su group and 31 days in the Placebo group.
- Consistent differences were observed in favor of the HZ/su group compared to the Placebo group in the AUC scores for the ZBPI worst pain score, ZBPI average pain score, and ZBPI ADL score for all of the time periods, i.e., 30, 90 and 182 days suggesting that the severity of disease was reduced in the HZ/su group compared with the Placebo group.
- Some differences were observed between HZ/su and Placebo groups, in favor of HZ/su, when analyzing the SF-36 and EQ-5D scales, particularly at Week 1 of the HZ episode. No consistent differences in favour of either group were observed at other timepoints suggesting that the largest differences between HZ/su and Placebo groups in the impact on QoL were observed in the first week of the HZ episode.
- The estimated HZ Disutility Score by age group and timepoint assessed using the EQ-5D in the Placebo Group was estimated as -0.3328 (95% CI: -0.4383, -0.2274) and -0.2406 (95% CI: -0.3035, -0.1778) on Day 0 in the age groups 18-49 YOA and ≥50 YOA, respectively suggesting a major impact on QoL due to the HZ episode for non-vaccinated subjects.

Immunogenicity results:

Humoral immunogenicity

Anti-gE specific humoral immune response overall

In autologous HCT recipients ≥ 18 YOA a strong anti-gE Ab response was elicited following a two dose-schedule of HZ/su (Month 2). From all timepoints evaluated, the highest immune responses were observed one month post-dose 2. The anti-gE Ab responses decreased one year post-dose 2 (Month 13) but persisted well above pre-vaccination levels for up to two years post-dose 2 (Month 25).

Post-vaccination, anti-gE GMCs at Months 1, 2, 13 and 25 were 1844.2 mIU/mL (95% CI: 1282.2 – 2652.4), 12753.2 mIU/mL (95% CI: 7973.0 – 20399.4), 3183.8 mIU/mL (95% CI: 1869.8 – 5421.2) and 2819.0 mIU/mL (95% CI: 1387.1 – 5729.1), respectively, for the HZ/su group. The MGI (versus Month 0) in the HZ/su group at Months 1, 2, 13 and 25 were 2.49 (95% CI: 1.78 – 3.49), 16.72 (95% CI: 10.01 – 27.92), 4.51 (95% CI: 2.58 – 7.89) and 4.35 (95% CI: 1.89 – 9.99), respectively. VRRs at Months 1, 2, 13 and 25 were 29.5% (95% CI: 19.7% - 40.9%), 67.1% (95% CI: 55.8% - 77.1%), 40.4% (95% CI: 27.0% - 54.9%) and 44.7% (95% CI: 28.6% - 61.7%), respectively. The adjusted GM ratio for HZ/su over placebo of anti-gE Ab concentrations at Month 2 was 21.56 (95% CI: 12.91 – 36.01) (Synopsis Table 3).

Synopsis Table 3: Adjusted geometric means and ratio for HZ/su over Placebo of anti-gE antibody ELISA concentrations at Month 2 (ATP cohort for Humoral-immunogenicity)

			Adjusted geometric mean			Adjusted geometric mean ratio			
				95% CI			95% CI		
Timing	**Group**	**N**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**	**P-value for the ratio**
PII(M2)	HZ/su	82	11227.7	6769.6	18621.7	21.56	12.91	36.01	<.0001
	Placebo	76	520.7	470.0	577.0	.	.	.	.

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
N = number of subjects in a given category with available results
LL = Lower Limit, UL = Upper Limit and CI = Confidence Interval
Confidence Interval (CI) were back transformed to original units
The p-value is relative to the null hypothesis Ho: Vaccine / Placebo = 1
PII(M2) = Post-vaccination Dose II (Month 2)

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Anti-gE specific humoral immune response by subgroup

The results obtained for the 18-49 YOA and ≥ 50 YOA strata consistently showed high anti-gE immune responses in the HZ/su group that remained above pre-vaccination levels up to two years post-dose 2.

The results of the analyses by underlying diseases (subjects with an underlying diagnosis of multiple myeloma or with all other diagnoses [including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T-cell lymphoma, acute myeloid leukemia, solid organ malignancies, etc.]) in autologous HCT recipients ≥ 18 YOA consistently showed high anti-gE immune responses in the HZ/su group.

Cell-mediated immunogenicity

gE-specific CMI overall

In autologous HCT recipients ≥ 18 YOA, strong gE-specific CMI responses were observed following two doses of HZ/su at one month post-dose 2 (Month 2). The highest immune responses were observed at one month post-dose 2; the observed gE-specific CMI responses were lower one year post-dose 2 (Month 13) but persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25).

In the HZ/su group, the observed median (min - max) frequency of gE-specific CD4[2+] T-cells (per 10^6 total CD4+ T-cells) was 48.9 (1.0 – 2469.7), 570.3 (1.0 – 14121.1), 6644.9 (1.0 – 73143.3), 1706.4 (1.0 – 17462.0) and 2294.4 (52.0 – 26020.4) at Months 0, 1, 2, 13 and 25, respectively. In the Placebo group, at all timepoints the observed median frequency of gE-specific CD4[2+] T-cells remained at pre-vaccination levels (point estimate of 65.0 at Month 0).

In the HZ/su group, the observed median (min - max) fold increase over pre-vaccination in the frequency of gE-specific CD4 [2+] T-cells was 8.2 (0.0 – 3486.5), 109.0 (0.0 – 24677.3), 43.6 (0.0 – 7502.6) and 50.9 (0.3 – 3126.4) at Months 1, 2, 13 and 25. In the Placebo group, the observed median fold increase over pre-vaccination in the frequency of gE-specific CD4[2+] T-cells (point estimate) was not higher than 2.1 at any timepoint.

In the HZ/su group, the VRR in the frequency of gE-specific CD4[2+] T-cells was 46.3% (95% CI: 30.7% - 62.6%), 92.9% (95% CI: 80.5% - 98.5%), 70.4% (95% CI: 49.8% - 86.2%) and 70.8% (95% CI: 48.9% - 87.4%) at Months 1, 2, 13 and 25. In the Placebo group, the VRR in the frequency of gE-specific CD4[2+] T-cells (point estimate) was not higher than 12.5% at any timepoint.

The exploratory group comparison at one month post-dose 2 (Month 2) showed a higher adjusted GM frequency of gE-specific CD4[2+] T-cells in the HZ/su group as compared to the Placebo group. The adjusted GM ratio (HZ/su group/Placebo group) was 64.36 (95% CI: 21.80 – 190.06) (Synopsis Table 4).

Synopsis Table 4: Adjusted geometric means and ratio of HZ/su over Placebo for gE-specific CD4[2+] T-cells frequencies at Month 2 (ATP cohort for Cell-Mediated Immunogenicity)

			Adjusted geometric mean			Adjusted geometric mean ratio			
				95% CI			95% CI		
Timing	**Group**	**N**	**Value**	**LL**	**UL**	**Value**	**LL**	**UL**	**P-value for the ratio**
PII(M2)	HZ/su	42	5397.0	4013.7	7231.8	64.36	21.80	190.06	<.0001
	Placebo	41	83.9	5.3	189.4	.	.	.	.

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
N = number of subjects in a given category with available results
LL = Lower Limit, UL = Upper Limit and CI = Confidence Interval
Confidence Interval (CI) were back transformed to original units
The p-value is relative to the null hypothesis Ho: Vaccine / Placebo = 1
PII(M2) = Post-vaccination Dose II (Month 2)

gE-specific CMI by subgroup

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

The results obtained in the 18-49 YOA and ≥ 50 YOA strata consistently showed in the HZ/su group gE-specific CMI responses above pre-vaccination levels at one month post-dose 2 (Month 2) that persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25).

The results obtained in autologous HCT recipients ≥ 18 YOA by underlying diseases (subjects with an underlying diagnosis of multiple myeloma or with all other diagnoses [including non-Hodgkin B-cell lymphoma, Hodgkin lymphoma, non-Hodgkin T-cell lymphoma, acute myeloid leukemia, solid organ malignancies, etc.]) consistently showed in the HZ/su group gE-specific CMI responses above pre-vaccination levels at one month post-dose 2 (Month 2) that persisted relative to pre-vaccination levels up to two years post-dose 2 (Month 25).

Safety results:

Unless otherwise specified, the analyses of AEs included both non-serious and serious AEs. The term "symptoms" in tables refers to AEs.

Overall

Any AEs during the 7-day (Days 0-6) post-vaccination period (dose 1 and dose 2 considered):

- Overall, at least one solicited or unsolicited AE (local or general) was reported for 88.8% and 57.1% of subjects in the HZ/su and Placebo groups, respectively.
- Overall, at least one grade 3 solicited or unsolicited AE (local or general) was reported for 22.2% and 6.8% of subjects in the HZ/su and Placebo groups, respectively.

*Solicited local **AEs** during the 7-day (Days 0-6) post-vaccination period (dose 1 and dose 2 considered):*

- Overall, at least one solicited local ***AE*** was reported for 85.8% and 10.4% of subjects in the HZ/su and Placebo groups, respectively. The most frequently reported solicited local ***AE*** in the HZ/su group was pain: 83.9% of subjects versus 9.3% of subjects in the Placebo group (Synopsis Table 5).
  - After dose 1 and dose 2, respectively, at least one solicited local ***AE*** was reported for 78.8% and 78.2% of subjects in the HZ/su group; and for 7.1% and 5.9% of subjects in the Placebo group.
- Overall, at least one grade 3 solicited local ***AE*** was reported for 14.2% and 0.3% of subjects in the HZ/su and Placebo groups, respectively.
  - After dose 1 and dose 2, respectively, at least one grade 3 solicited local ***AE*** was reported for 7.4% and 10.5% of subjects in the HZ/su group; and for 0.3% and 0.0% of subjects in the Placebo group.
- Regarding the duration of solicited local ***AEs*** during the 7-day post-vaccination period, overall/dose, the median duration for pain was 3.0 days in the HZ/su group and 1.0 day in the Placebo group. ***(Amended 02 May 2019)***

Synopsis Table 5: Incidence of solicited local symptoms reported during the 7-day (Days 0-6) post-vaccination period overall subjects and overall doses (Total Vaccinated Cohort)

		HZ/su					Placebo				
					95% CI					95% CI	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/dose											
Pain	All	1736	1326	76.4	74.3	78.4	1724	101	5.9	4.8	7.1
	Grade 3	1736	122	7.0	5.9	8.3	1724	3	0.2	0.0	0.5
Redness (mm)	All	1736	418	24.1	22.1	26.2	1724	9	0.5	0.2	1.0
	>100	1736	31	1.8	1.2	2.5	1724	0	0.0	0.0	0.2
Swelling (mm)	All	1736	233	13.4	11.9	15.1	1724	10	0.6	0.3	1.1
	>100	1736	13	0.7	0.4	1.3	1724	0	0.0	0.0	0.2
Overall/subject											
Pain	All	901	756	83.9	81.3	86.2	892	83	9.3	7.5	11.4
	Grade 3	901	99	11.0	9.0	13.2	892	3	0.3	0.1	1.0

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Redness (mm)	All	901	301	33.4	30.3	36.6	892	9	1.0	0.5	1.9
	>100	901	28	3.1	2.1	4.5	892	0	0.0	0.0	0.4
Swelling (mm)	All	901	168	18.6	16.2	21.3	892	9	1.0	0.5	1.9
	>100	901	13	1.4	0.8	2.5	892	0	0.0	0.0	0.4

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
For overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom
95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit

*Solicited general **AEs** during the 7-day (Days 0-6) post-vaccination period (dose 1 and dose 2 considered):*

- Overall, at least one solicited general ***AE*** was reported for 75.2% and 50.9% of subjects in the HZ/su and Placebo groups, respectively. The most frequently reported solicited general ***AEs*** in the HZ/su group were fatigue (56.4% versus 38.0% in the Placebo group) and myalgia (53.7% versus 26.2% in the Placebo group) (Synopsis Table 6). At least one solicited general ***AE*** with causal relationship to vaccination as per investigator assessment was reported for 42.1% and 16.8% of subjects in the HZ/su and Placebo groups, respectively.
  - After dose 1 and dose 2, respectively, at least one solicited general ***AE*** was reported for 59.2% and 66.0% of subjects in the HZ/su group; and for 41.9% and 36.8% of subjects in the Placebo group. After dose 1 and dose 2, respectively, at least one solicited general ***AE*** with causal relationship to vaccination as per investigator assessment was reported for 26.5% and 34.6% of subjects in the HZ/su group; and for 11.8% and 10.2% of subjects in the Placebo group.
- Overall, at least one grade 3 solicited general ***AE*** was reported for 13.2% and 6.0% of subjects in the HZ/su and Placebo groups, respectively. At least one grade 3 solicited general ***AE*** with causal relationship to vaccination as per investigator assessment was reported for 7.8% and 1.0% of subjects in the HZ/su and Placebo groups, respectively.
  - After dose 1 and dose 2, respectively, at least one grade 3 solicited general ***AE*** was reported for 5.8% and 10.8% of subjects in the HZ/su group; and for 3.1% and 4.0% of subjects in the Placebo group. After dose 1 and dose 2, respectively, at least one grade 3 solicited general ***AE*** with causal relationship to vaccination as per investigator assessment was reported for 3.3% and 6.3% of subjects in the HZ/su group; and for 0.6% and 0.5% of subjects in the Placebo group.
- Regarding the duration ***of solicited*** general ***AEs*** during the 7-day post-vaccination period, overall/dose, the median duration for fatigue and myalgia was 3.0 days for both ***AE***s in the HZ/su group and 5.0 and 4.0 days, respectively, in the Placebo group. ***(Amended 02 May 2019)***

Synopsis Table 6 - Incidence of solicited general symptoms reported during the 7-day (Days 0-6) post-vaccination period overall subjects and overall doses (Total Vaccinated Cohort)

		HZ/su					**Placebo**				
					95% CI					**95% CI**	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Overall/dose											
Fatigue	All	1732	751	43.4	41.0	45.7	1727	494	28.6	26.5	30.8
	Grade 3	1732	78	4.5	3.6	5.6	1727	36	2.1	1.5	2.9
	Related	1732	277	16.0	14.3	17.8	1727	96	5.6	4.5	6.7
	Grade 3 Related	1732	41	2.4	1.7	3.2	1727	7	0.4	0.2	0.8

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium		**Name of finished product:** HZ/su					**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)				
Gastrointestinal symptoms	All	1732	292	16.9	15.1	18.7	1727	232	13.4	11.9	15.1
	Grade 3	1732	19	1.1	0.7	1.7	1727	19	1.1	0.7	1.7
	Related	1732	92	5.3	4.3	6.5	1727	35	2.0	1.4	2.8
	Grade 3 Related	1732	5	0.3	0.1	0.7	1727	1	0.1	0.0	0.3
		HZ/su					**Placebo**				
					95% CI					**95% CI**	
Symptom	**Type**	**N**	**n**	**%**	**LL**	**UL**	**N**	**n**	**%**	**LL**	**UL**
Headache	All	1732	388	22.4	20.5	24.4	1727	209	12.1	10.6	13.7
	Grade 3	1732	26	1.5	1.0	2.2	1727	11	0.6	0.3	1.1
	Related	1732	146	8.4	7.2	9.8	1727	52	3.0	2.3	3.9
	Grade 3 Related	1732	15	0.9	0.5	1.4	1727	1	0.1	0.0	0.3
Myalgia	All	1732	714	41.2	38.9	43.6	1727	323	18.7	16.9	20.6
	Grade 3	1732	64	3.7	2.9	4.7	1727	20	1.2	0.7	1.8
	Related	1732	378	21.8	19.9	23.8	1727	97	5.6	4.6	6.8
	Grade 3 Related	1732	39	2.3	1.6	3.1	1727	2	0.1	0.0	0.4
Shivering	All	1732	301	17.4	15.6	19.2	1727	132	7.6	6.4	9.0
	Grade 3	1732	35	2.0	1.4	2.8	1727	7	0.4	0.2	0.8
	Related	1732	158	9.1	7.8	10.6	1727	43	2.5	1.8	3.3
	Grade 3 Related	1732	26	1.5	1.0	2.2	1727	1	0.1	0.0	0.3
Temperature/ (*) (°C)	All	1732	210	12.1	10.6	13.8	1727	56	3.2	2.5	4.2
	>39.5	1732	3	0.2	0.0	0.5	1727	1	0.1	0.0	0.3
	Related	1732	113	6.5	5.4	7.8	1727	15	0.9	0.5	1.4
	>39.5 Related	1732	3	0.2	0.0	0.5	1727	0	0.0	0.0	0.2
Overall/subject											
Fatigue	All	901	508	56.4	53.1	59.6	894	340	38.0	34.8	41.3
	Grade 3	901	66	7.3	5.7	9.2	894	31	3.5	2.4	4.9
	Related	901	210	23.3	20.6	26.2	894	79	8.8	7.1	10.9
	Grade 3 Related	901	35	3.9	2.7	5.4	894	7	0.8	0.3	1.6
Gastrointestinal symptoms	All	901	238	26.4	23.6	29.4	894	183	20.5	17.9	23.3
	Grade 3	901	18	2.0	1.2	3.1	894	17	1.9	1.1	3.0
	Related	901	79	8.8	7.0	10.8	894	30	3.4	2.3	4.8
	Grade 3 Related	901	5	0.6	0.2	1.3	894	1	0.1	0.0	0.6
Headache	All	901	302	33.5	30.4	36.7	894	166	18.6	16.1	21.3
	Grade 3	901	26	2.9	1.9	4.2	894	10	1.1	0.5	2.0
	Related	901	123	13.7	11.5	16.1	894	46	5.1	3.8	6.8
	Grade 3 Related	901	15	1.7	0.9	2.7	894	1	0.1	0.0	0.6
Myalgia	All	901	484	53.7	50.4	57.0	894	234	26.2	23.3	29.2
	Grade 3	901	56	6.2	4.7	8.0	894	19	2.1	1.3	3.3
	Related	901	279	31.0	28.0	34.1	894	83	9.3	7.5	11.4
	Grade 3 Related	901	32	3.6	2.4	5.0	894	2	0.2	0.0	0.8
Shivering	All	901	237	26.3	23.5	29.3	894	115	12.9	10.7	15.2
	Grade 3	901	35	3.9	2.7	5.4	894	7	0.8	0.3	1.6

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

	Related	901	131	14.5	12.3	17.0	894	38	4.3	3.0	5.8
	Grade 3 Related	901	26	2.9	1.9	4.2	894	1	0.1	0.0	0.6
Temperature/ (*) (°C)	All	901	183	20.3	17.7	23.1	894	50	5.6	4.2	7.3
	>39.5	901	3	0.3	0.1	1.0	894	1	0.1	0.0	0.6
	Related	901	101	11.2	9.2	13.5	894	15	1.7	0.9	2.8
	>39.5 Related	901	3	0.3	0.1	1.0	894	0	0.0	0.0	0.4

HZ/su = Herpes Zoster sub-unit vaccine group
Placebo = Placebo group
For Overall/subject:
N = number of subjects with at least one documented dose
n/% = number/percentage of subjects reporting the symptom at least once
For Overall/dose:
N = number of documented doses
n/% = number/percentage of doses followed by at least one type of symptom

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

95%CI = Exact 95% confidence interval; LL = lower limit, UL = upper limit
All = all subjects who have experienced the symptom
*Temperature is measured by oral, axillary, rectal or tympanic routes
Fever is defined as temperature ≥ 37.5°C for oral, axillary or tympanic route, or ≥ 38.0°C for rectal route

Unsolicited AEs during the 30-day (Days 0-29) post-vaccination period (dose 1 and dose 2 considered):

- Overall, 360 (39.0%) subjects in the HZ/su group and 353 (38.2%) subjects in the Placebo group reported at least one unsolicited AE. Most frequent unsolicited AEs in the HZ/su group were upper respiratory tract infection (28 subjects [3.0%], reported for 30 subjects [3.2%] in the Placebo group), neutropenia (24 subjects [2.6%], reported for 25 subjects [2.7%] in the Placebo group),viral upper respiratory tract infection (23 subjects [2.5%], reported for 30 subjects [3.2%] in the Placebo group), and cough (22 subjects [2.4%], reported for 14 subjects [1.5%] in the Placebo group-. Most frequent unsolicited AEs in the Placebo group were upper respiratory tract infection, viral upper respiratory tract infection, neutropenia, cough (see incidence above) and edema peripheral (18 subjects [1.9%]; reported for 11 subjects [1.2%] in the HZ/su group).
- Overall, 60 (6.5%) subjects in the HZ/su group and 47 (5.1%) subjects in the Placebo group reported at least one grade 3 unsolicited AE. Most frequent grade 3 unsolicited ***AEs*** in the HZ/su and Placebo groups, respectively, were neutropenia (10 subjects [1.1%] and 4 subjects [0.4%], respectively) and plasma cell myeloma (4 subjects [0.4%] and 7 subjects [0.8%], respectively). Additionally, grade 3 diarrhea was frequently reported in the Placebo group (4 subjects [0.4%], reported by 2 subjects [0.2%] in the HZ/su group). ***At least one grade 3 non-serious unsolicited AE was reported by 28 (3.0%) subjects in the HZ/su group and 22 (2.4%) subjects in the Placebo group within 30 days post-vaccination.***
- Overall, 31 (3.4%) subjects in the HZ/su group and 23 (2.5%) subjects in the Placebo group reported at least one unsolicited AEs with causal relationship to vaccination ***as per investigator assessment***.
- Overall, 6 (0.7%) subjects in the HZ/su group and 5 (0.5%) subjects in the Placebo group reported at least one grade 3 unsolicited AEs with causal relationship to vaccination as per investigator assessment. ***At least one grade 3 non-serious unsolicited AE with causal relationship to vaccination as per investigator assessment was reported by 6 (0.7%) subjects in the HZ/su group and 4 (0.4%) subjects in the Placebo group within 30 days post-vaccination. (Amended 02 May 2019)***
- Overall, 221 (24.0%) subjects in the HZ/su group and 192 (20.8%) subjects in the Placebo group reported at least one unsolicited AEs with medically attended visit.

SAEs, (S)AEs leading to withdrawal, pIMDs and relapse cases

Overall, there were no apparent differences in the percentage of subjects reporting SAEs, SAEs reported with causal relationship to vaccination as per investigator assessment and fatal SAEs between study groups in the different time periods evaluated. Overall, there was no cluster in the nature of the pIMDs reported and no safety concern was highlighted. No imbalance between the HZ/su and Placebo groups was observed regarding subjects withdrawn due to a non-serious AE or SAEs (data collected up Visit 5 [Month 25]).

SAEs:

- The number (%) of subjects with at least one SAE in the HZ/su group was 68 (7.4%) and 263 (28.5%) when reported from first vaccination up to 30 days post-last vaccination and up to 365 days, respectively; and in the Placebo group 66 (7.1%) and 241 (26.1%), respectively.
- The number (%) of subjects with at least one SAE with causal relationship to vaccination as per investigator assessment in the HZ/su group was 1 (0.1%) and 3 (0.3%) when reported from first vaccination up to 30 days post-last vaccination and up to 365 days post-last vaccination, respectively; and in the Placebo group 3 (0.3%) and 4 (0.4%), respectively. No additional SAEs

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

with causal relationship to vaccination as per investigator assessment were reported in the period between 365 days post-last vaccination up to study end.

Fatal SAEs:

- ***From first vaccination up to 30 days post-last vaccination, the number (%) of subjects with onset of fatal SAEs was*** 20 (2.2%) ***in the HZ/su group*** and 19 (2.1%) ***in the Placebo group. During this period, 1 (0.1%) subject in the HZ/su group and 3 (0.3%) subjects in the Placebo group died.***
- ***From first vaccination up to 365 days post-last vaccination, the number (%) of subjects with onset of fatal SAEs was*** 77 (8.4%) ***in the HZ/su group and*** 79 (8.5%) ***in the Placebo group. During this period***, ***51 (5.5%) subjects in the HZ/su group and 49 (5.3%) subjects in the Placebo group died.***
- ***From first vaccination up to study end, the number (%) of subjects with onset of fatal SAEs was 118 (12.8%) in the HZ/su group and 124 (13.4%) in the Placebo group. During this period, the same number of subjects died.*** There were no fatal SAEs reported with causal relationship to vaccination by the investigator during the entire study period. ***(Amended 02 May 2019)***

SAEs and AEs leading to withdrawal from study

- From first vaccination until Visit 4, there were 132 subjects withdrawn from the study due to at least one SAE (65 and 67 subjects in the HZ/su and Placebo groups, respectively). There were 28 subjects withdrawn from the study due to at least one non-serious AE (14 in each group).
- Between Visit 4 and Visit 5, there were 73 subjects withdrawn from the study due to at least one SAE (35 subjects in the HZ/su group and 38 subjects in the Placebo group). There were 12 subjects withdrawn from the study due to at least one non-serious AE (8 subjects in the HZ/su group and 4 subjects in the Placebo group).
- Between Visit 5 and the cut-off date for final analysis, there were 26 subjects in the HZ/su group and 23 subjects in the Placebo group withdrawn from the study due a fatal SAE.

pIMDs:

- The number of subjects with at least one pIMD up to 365 days post-last vaccination was 13 (1.4%) and 8 (0.9%) in the HZ/su and Placebo groups, respectively. Most frequent pIMDs (classification by PT) were psoriasis (reported for 2 [0.2%] in the HZ/su group) and interstitial lung disease (reported for 2 [0.2%] subjects in the Placebo group). All other pIMDs were reported by no more than one subject in any group.

Relapse cases:

- The number of subjects with at least one relapse case over the entire study period was 239 (25.9%) and 253 (27.4%) in the HZ/su and Placebo groups, respectively.

Pregnancies:

- A total of 14 pregnancy outcomes were reported in 11 subjects during the study period (7 subjects in the HZ/su group and 4 subjects in the Placebo group). In all cases, exposure to HZ/su / placebo occurred before pregnancy onset. From the 7 subjects in the HZ/su, there were 7 live infants with no apparent congenital anomalies and 1 elective termination.

By age strata **(**18-49 YOA and ≥ 50 YOA)

Overall, by age, there ***was*** no apparent difference in the frequency of solicited ***AEs*** between 18-49 YOA and ≥50 YOA groups. ***(Amended 02 May 2019)***

Safety results (unsolicited AEs, SAEs ***[including fatal SAEs, either by date of onset of fatal SAE or date of death]***, pIMDs, relapse cases) obtained by age strata were in line with safety results reported overall. For both age strata, there were no apparent differences between HZ/su and Placebo groups.

Important safety information received after the data lock point (database freeze date):
No important additional safety information was available after the data lock point.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Conclusions:

Except for the analyses of the primary endpoint, all the other analyses (of secondary and tertiary endpoints including by subgroup analyses) were exploratory. The study was not designed to draw confirmatory conclusions on these analyses as no control of type I error was done.

Efficacy

The overall HZ VE in autologous HCT recipients ≥ 18 YOA (mTVC) was 68.17% (95% CI: 55.56% - 77.53%; P<0.0001) after an approximate median follow-up time of 21 months (approximately 22 months in the HZ/su group and approximately 20 months in the Placebo group). The primary objective of the study was met as statistically significant VE (68.17%, p<0.0001) was demonstrated in the prevention of HZ in autologous HCT recipients ≥ 18 YOA with a LL of the 95% CI (55.56%) above 0%.

Results from secondary objectives suggest that HZ/su can prevent PHN and HZ-related complications in autologous HCT recipients ≥ 18 YOA, and can reduce the duration of severe 'worst HZ associated pain' in subjects of this population with confirmed HZ.

Results from tertiary objectives suggest also an effect of HZ/su against HZ during 1 year post-HCT and an effect against HZ–related hospitalizations in autologous HCT recipients ≥ 18 YOA.

Name of company: GlaxoSmithKline Biologicals, SA, Rixensart, Belgium	**Name of finished product:** HZ/su	**Name of active substance:** Varicella Zoster Virus glycoprotein E (VZV gE)

Quality of Life

Consistent differences were observed in favor of the HZ/su group compared to the Placebo group when measuring pain associated with the HZ episode using the ZBPI worst and average pain scores, the derived ZBPI time to resolution of clinically significant pain, and Burden of illness/Burden of interference scores, suggesting that the severity of disease was reduced in the HZ/su group compared with the Placebo group.

Immunogenicity

In autologous HCT recipients ≥ 18 YOA, HZ/su elicited strong anti-gE Ab responses and gE-specific CMI responses following 2 doses of HZ/su at one month post-dose 2 (Month 2) that persisted up to two years post-dose 2 (Month 25) relative to pre-vaccination levels.

Safety

In autologous HCT recipients ≥ 18 YOA, HZ/su was shown to have a clinically acceptable profile. No safety concern was identified.

Overall, a higher percentage of subjects reported solicited local and general AEs (any grade, grade 3, related and grade 3 related as per investigator assessment) during the 7-day post-vaccination period in the HZ/su group compared to the Placebo group. In the HZ/su group, the most frequently reported solicited local ***AE*** observed was pain, and the most frequently reported solicited general ***AEs*** were fatigue and myalgia.

Overall, there were no apparent differences between HZ/su and Placebo groups for unsolicited AEs during the 30-day post-vaccination period.

There were no apparent differences between HZ/su and Placebo groups in the percentage of subjects with SAEs, SAEs reported with causal relationship to vaccination as per investigator assessment, or fatal SAEs reported ***by either date of onset of the fatal SAE or date of death*** during the study. ***(Amended 02 May 2019)***

No fatal SAE with causal relationship to vaccination (as per investigator assessment) was reported in the study.

There was no cluster in the nature of the pIMDs reported and no safety concern was identified.

There were no apparent differences between HZ/su and Placebo groups in the percentage of subjects with relapse cases reported during the study.

There was no apparent imbalance between the HZ/su and the Placebo groups regarding subjects withdrawn from the study due to SAEs or AEs.

References:

Miettinen OS, Nurminen M. Comparative analysis of two rates. *Stat Med.* 1985; 4: 213-226.

Date of Report: ***Amendment 1 Final, 02 May 2019***

Appendix 1 to Synopsis for study ZOSTER-002 (115523)

Overview of Protocol Amendments

Excerpt from protocol including final amendment version 07 dated 24-July-2015

Protocol Amendment 1 Rationale

Amendment number: Amendment 1

Rationale/background for changes:

The following updates have been made:

- To address a request from FDA, the conditions for final triggered analysis include that all subjects need to have completed Visit 4 (Month 13). Aligned with this update, the definition of study end has been clarified, i.e., study end will take place when the conditions for final triggered analysis are met and follow-up is completed for each suspected HZ case that occurs up to and including the cut-off date for final analysis. The synopsis, Sections 3, 5.4.2.3, 5.4.2.4, 5.5, 5.6.4.12, 5.6.4.16 and 8.3.1 have been updated accordingly. A clarification has been added in the Synopsis, Sections 3 and 10.7.1 that the end of study analysis, if performed, will be descriptive.
- To address a request from FDA, the following study objectives (tertiary objectives) have been added in the Synopsis and in Section 2.3.
  - To evaluate VE in the prevention of HZ in autologous HCT recipients 18 years of age and older when all subjects reach 1 year post-HCT;
  - To evaluate VE in the prevention of PHN in autologous HCT recipients 18 years of age and older with confirmed HZ.

  Endpoints related to these objectives have been added in the Synopsis and in Section 10.3 and information regarding additional statistical analyses in Sections 10.8.2.1 and 10.8.2.2. Wording in Section 5.4.2.1.3 has been updated accordingly.
- To address a request from FDA, the allowed interval between Visit 2 (Month 1, the day of the second dose of study vaccine/placebo) and Visit 4 (Month 13, approximately 12 months after the second dose of study vaccine/placebo) has been modified (Section 5.5).
- A clarification has been added that the date of Visit 2 (i.e., the date of the second dose of study vaccine/placebo) is taken as reference to determine the applicable allowed interval between Visit 2 and Visits 3, Visit 2 and Visits 4, and Visit 2 and Visits 5, respectively (Sections 5.5 and 8.3.1), and that visit numbers are referred to interchangeably with their month designations throughout the protocol (Month 0 refers to Visit 1, Month 1 refers to Visit 2, etc). For example, all SAEs are to be reported until Visit 4 (Month 13). Visit 4 is used to indicate approximately 12 months post second vaccination (Section 3). Wording in Section 8.3.1 has been updated accordingly.
- A clarification has been added in Section 10.7.1 regarding the efficacy, immunogenicity and safety objectives applicable for the interim analysis and the final triggered analysis, respectively.
- A clarification has been added in Section 4.3 that pneumococcal conjugate vaccines can also be administered within the window specified for licensed non-replicating vaccines.
- In alignment with Section 6.6.1, the time window for recording of administration of any vaccine against varicella has been specified in Section 6.6.2.
- A typographical error has been corrected in Section 10.8.2.

Protocol Amendment 2 Rationale

Amendment number: Amendment 2

Rationale/background for changes:

- At the European Medicines Agency's (EMA) request, GSK Biologicals has updated its procedure for emergency unblinding during the conduct of a clinical study. According to the revised procedure, the responsibility and the decision to break the treatment code in emergency situations resides solely with the investigator and consequently, the investigator will have full authority to break the treatment code. Section 8.8 and the Sponsor Information page has been updated accordingly.
- To improve data collection, changes have been made in instructions for Zoster Brief Pain Inventory (ZBPI) completion. Subjects should start completing a ZBPI questionnaire with the appearance of symptoms suggestive of HZ and continue daily with ZBPI completion, instead of completing retrospectively a ZBPI questionnaire at Visit HZ-1 for the elapsed time between the HZ onset and 24 hours before Visit HZ-1 (Sections 5.4.1, 5.4.2.3, 5.5, 5.6.4.13 and 10.8.2.5);
- On request from some sites, for women of childbearing potential, prior to vaccination a serum pregnancy test instead of a urine pregnancy test can be performed if this is required by country, local or ethics committee regulations. In case a serum pregnancy test is required, a blood sample will be collected and used for the test as per local guidance (Synopsis, Sections 3, 5.5, 5.6.3.4, 5.6.4.5 and 5.7.2);
- A clarification has been added that certain required signatories on the Protocol Amendment Investigator Agreement page are country-specific;
- Study entry occurs at the pre-vaccination visit. Therefore it has been detailed that subjects should be 18 years of age or above at study entry (Section 4.2, Section 12.1);
- For clarification, further details have been added regarding the prophylactic antiviral therapy to take into account as exclusion criterion at study entry (Section 4.3) and as medication that may lead to the elimination of a subject from ATP analyses (Section 6.6.1). Sections 5.4.3 (Standard of care) and 6.6.2 (Time window for recording concomitant medication/vaccination in the eCRF) have been updated accordingly;
- To increase representativity of the immune data, a randomization algorithm to assign subjects to the humoral and CMI sub-cohorts has been introduced (Section 5.2.3) to avoid selection bias.

- The circumstances where the investigator has the option to collect up to three additional rash samples after Visit HZ-1 at an unscheduled visit at the time of Contact HZ-2 at the latest (i.e., <3 lesions present or only papules present) has been clarified in Sections 5.4.2.3, 5.5, 5.7.2 and Appendix 2;
- The wording in Section 6.3 has been updated to align with the current instructions for reconstitution of the gE/AS01$_B$ study vaccine and placebo;
- To align with the related exclusion criterion, and additional example has been added regarding licensed non-replicating vaccines that may be administered up to 8 days prior to dose 1 or dose 2 and/or at least 14 days after any dose of study vaccine/placebo (Section 6.6.1);
- For clarification, the definition of an intercurrent medical condition has been further refined (Section 6.7);
- For clarity, it has been specified that information regarding the medical attention subjects may receive for an adverse event (AE) or serious adverse event (SAE) they experience during the applicable reporting period needs to be captured (Sections 8.3.1 and 8.3.2.4);
- For clarification, it has been detailed that the reporting period for SAEs that are related to the investigational product and for SAEs that are related to study participation or are related to a concurrent GSK medication/vaccine or any fatal SAE, ends when the subject is discharged from the study (Section 8.3.1);
- To harmonise across different clinical studies being performed with the same herpes zoster gE/AS01$_B$ candidate vaccine, Section 10.6.4 has been updated to include modified derived data for CMI;
- For clarity, information regarding country-specific age of legal consent has been grouped in a separate Section 12.1. The numbering of the other subsections of Section 12 has been updated accordingly. To align with country-specific requirements in Canada, details have been added regarding applicable age of legal consent.
- The list of contributing authors has been updated (Title page)
- Typographical errors have been correction in Sections 5.4.2.2, 12.1 and 12.4.

Protocol Amendment 3 Rationale

Amendment number: Amendment 3

Rationale/background for changes:

The following updates have been made:

- At the Medicines and Healthcare products Regulatory Agency (MHRA) request (MHRA Reference 19842/0215/001-0001), the occurrence of herpes zoster (HZ) with characteristic Varicella Zoster Virus [VZV] or HZ rash (protocol criterion 1) and postherpetic neuralgia (PHN) associated with a case of HZ will be considered as adverse events (AEs). These events will be recorded in HZ-specific eCRF screens. If these occurrences meet the definition of a serious adverse event (SAE), then they will be reported as such. (Sections 5.4.2.1.3, 5.4.2.3, 6.7, 8.1.1, 8.2.1, 8.3.1 and 8.4.1)
- As the occurrence of HZ and PHN are efficacy endpoints, cases of HZ with characteristic VZV or HZ rash and PHN associated with a case of HZ will be considered Population-Related Events (PREs). If they meet the definition of a SAE, they will be reported via the specific SAE screens only if they meet the criteria for expedited reporting (Sections 5.4.2.1.1, 5.4.2.1.3, 5.4.2.3, 8.1.1, 8.2.1, 8.3.1 and 8.4.1)
- Cases of HZ without characteristic VZV or HZ rash (protocol criterion 2) will continue to be reported as SAEs. It will be added that they will be specified on the SAE screen to be related to HZ (and not "a case of HZ without characteristic VZV or HZ rash") (Sections 5.4.2.1.1, 5.4.2.4 and 8.3.1)
- HZ complications different from PHN will continue to be reported as AEs or SAEs (as appropriate). It will be added that they will be specified on the AE or SAE screen to be related to HZ (and not as "a HZ complication"). (Section 8.3.1)
- Minor typographical errors have been corrected throughout the document

Protocol Amendment 4 Rationale

Amendment number: Amendment 4

Rationale/background for changes:

The following updates have been made:

- In response to FDA/CBER's 25MAY2012 comments on the protocol, cases of suspected HZ will not be considered a confirmed case of HZ for the efficacy analysis if they potentially could constitute a primary VZV infection (varicella). For subjects born in 1980 or later or before 1980 in a tropical region, and with no serological evidence of prior VZV infection at the time of Visit 1, a case of suspected HZ with a disseminated onset or a VZV infection without characteristic rash (criterion 2) may in reality represent a primary VZV infection. For such subjects, blood samples collected at Visit 1 (prior to vaccination) will now be tested for VZV serological status. (Sections 5.4.2.1.2, 5.5, 5.7.2, 5.7.3, 5.7.4, Appendix 1, Appendix 2)
- In response to FDA/CBER's 25MAY2012 comments on the protocol, it is now been added that pIMDs, relapses and HZ complications other than PHN may be serious AEs. (Section 8.5.1)
- In response to FDA/CBER's 25MAY2012 comments on the protocol, clarifications have been made to indicate what study procedures the subject would have to complete if a case which had been clinically diagnosed as HZ is no longer considered HZ by the investigator. (Section 5.4.2.3)
- In response to FDA/CBER's 25MAY2012 comments on the protocol, clarifications have been made to explain when follow-up of HZ with characteristic VZV or HZ rash is completed for cases accrued close to the end of the study. Modifications have been made to increase the likelihood of detecting cases of PHN occurring close to the end of the study. (Synopsis and Sections 3, 5.4.2.3, 5.4.2.4, 5.6.4.12, 5.6.4.16, 10.7.1)
- In response to FDA/CBER's 25MAY2012 comments on the protocol, clarifications have been made to indicate that illiterate subjects should have a designated person to provide assistance with the "real time" completion of questionnaires and diary cards. (Section 5.4.1)
- Table 15 (Study vaccine/placebo) was modified to clarify that the number of doses refers to the treatment, not the individual product
- On request from a local site, the age of legal consent in Malaysia being 18 years, Section 12.1 has been updated and Malaysia has been deleted from the listed countries
- A definition for 'attending physician' has been added in the Glossary of Terms to avoid confusion as any practitioner regardless of whether he/she is associated with a clinic/hospital or private may be involved in the diagnosis of suspected HZ
- Minor typographical errors have been corrected throughout the document

Protocol Amendment 5 Rationale

Amendment number: Amendment 5
Rationale/background for changes: The following updates have been made: • To address a concern of the Independent Data Monitoring Committee (IDMC), it has been specified that thrombocytopenia that in the judgment of the investigator would make intramuscular injection unsafe, constitutes a contraindication to administration of gE/AS01$_B$ study vaccine or placebo at that point in time (Section 6.5). The wording 'subsequent ' has been removed from the title of the section to indicate that the section also includes contraindications to be checked prior to the first vaccination. The order of the paragraphs has been changed to describe firstly the contraindications to be checked prior to the first and second vaccination, and secondly the absolute contraindications to be checked prior to the second vaccination. • In a footnote to the study design overview diagram (Section 3) and in a footnote to the List of study procedures (Section 5.5, Table 5) it has been clarified that each subject will be followed at least until he/she completes Visit 4. If conditions for study end are met, monthly contacts after Visit 4, Visit 5, and monthly contacts after Visit 5 may not take place in some subjects. A typographical error has been corrected. • Typographical errors have been corrected in Section 5.4.3.2 and Section 10.4.4 (Table 24).

Protocol Amendment 6 Rationale

Amendment number: Amendment 6

Rationale/background for changes:

- The randomization system (SBIR application) takes into account minimization factors for the randomized allocation of subjects into the study groups. These factors are taken into account by the system to decrease the risk of having unbalanced groups in the subjects' characteristics at baseline and in this way increase the robustness of the groups' comparison. During the set-up of the SBIR application, the minimization factors center and gender were included but were not specified in the protocol. They have now been specified in the protocol (Section 3, Section 5.2.2.2).
- The sample size increase is the result of the review of original study assumptions related to incidence rate of herpes zoster cases after autologous stem cell transplant and recalculation of the non evaluability rate of subjects based on observed data. The increase in the sample size is needed to ensure accrual of the necessary number of cases needed to perform the finalanalysis. Furthermore, this protocol amendment allows earlier termination of enrolment if the target number of HZ cases for the final analysis is reached (Section 3, Table 1, Section 4.1, Section 10.4.4, and Table 24).
- The number of HZ cases required to trigger the interim analysis has been increased from 46 to 60. This increases the probability to demonstrate vaccine efficacy at the moment of the interim analysis, while maintaining the alpha spent for the interim analysis at an acceptable level (Section 10.4.4, Table 24, Section 10.7.2)
- List of potential immune-mediated diseases has been updated (Section 8.1.5.1, Table 19).
- The cut-off of the gE-specific ELISA assay has been changed from 18 to 97 mIU/mL. Background signal has been measured with the anti-gE ELISA on samples from Varicella Zoster Virus (VZV) naïve paediatric subjects. This observation of background signal on VZV naïve samples was not part of the original validation of the assay and establishment of the assay cut-off. Background signal measured with the anti-gE ELISA has no impact on Zoster project clinical conclusions as the vast majority of the samples (at all timepoints) have high titers well above the unspecific response level measured on VZV naïve samples from Measles, Mumps, Rubella and Varicella (MMRV) studies and Zoster vaccine responses are very robust. However this finding triggered re-evaluation of the assay cut-off. Based on complementary validation experiments performed in line with Clinical and Laboratory Standards Institute (CLSI) guidelines and taking into account internal company guidelines the technical and seropositivity cut-off has been set at 97 mIU/mL. (Section 5.7.3, Table 10, and Appendix 1).
- Under revised local law in South Korea as of July 2013, the legal adult age was changed from ≥20 years old to ≥19 years old (Section 12.1).
- Minor edits in other sections were made for clarification.

Protocol Amendment 7 Rationale

Amendment number: Amendment 7

Rationale/background for changes:

- The interim analyses (IA) for efficacy, safety and immunogenicity have been cancelled. This decision was taken considering there are no longer scientific grounds to perform an interim analysis:
  - There were no stopping rules foreseen in the protocol based on the results of the efficacy IA. As the trigger for the efficacy IA was reached earlier than initially expected, vaccine efficacy (VE) from the IA would pertain to a limited follow-up time for a significant part of the population. In addition, the planned combined interim analysis for immunogenicity and safety will only be available in 2016. Therefore, it is not possible to perform a benefit/risk assessment for this population at the time of efficacy IA results.
  - Although no direct extrapolation of results can be drawn from another population, the high rate of VE reported in the older adult population [Lal, 2015] with the same candidate vaccine, could potentially translate to a high VE rate in the Zoster-002 population. As the efficacy IA would pertain to a limited follow-up time, it would be difficult to interpret these data and the need for more mature data would be indispensable.
- Due to the cancellation of the efficacy interim analysis, the type I error (alpha) used for final analysis (FA) has changed from 4.4% to 5% (combining both previously calculated alpha for interim and final analysis). This lead to a change of the two-sided confidence interval for final analysis from 95.6% to 95.0%.
- As the final analysis is expected to be triggered by last subject having Visit 4, it is anticipated that some subjects from the sub-cohorts for CMI and humoral immunogenicity will not have reached their Visit 5 time point for their last blood sampling. As the end of study criteria are triggered by the FA data cut-off, CMI and humoral immunogenicity analysis blood sampling will not be performed for these subjects at this timepoint. Sections related to sampling and analysis have been modified.
- The intervals between vaccinations (dose 1 to dose 2) and between dose 2 and blood sampling at Visit 3 (i.e. the 1 month post dose 2 visit) for inclusion in the According to Protocol cohort for immunogenicity/persistence phase are being enlarged to respectively 30-84 days and 21-63 days. The observation and interpretation of the immunogenicity/persistence data are not anticipated to be compromised by this modification. The increased flexibility will allow meaningful analysis of the data collected in this immunocompromised populations, where the underlying disease and implications of its treatment (such as cancer treatment schedule, side effects of the concomitant treatment) lead to a higher number of out of window visits compared to what is observed in a healthy population. (Section 10.5.5)
- Other minor changes.

Appendix 2 to Synopsis for study ZOSTER-002 (115523)

List of study sites

Worldwide Study Centres

Country Name	Principal Investigator Full Name	Clinical Site Institution Name	Clinical Site Street	inical Site ZIP Co	Clinical Site City
Australia	Gottlieb, David	Westmead Hospital	Cnr Hawkesbury & Darcy Rds	2145	Westmead
Australia	Grigg, Andrew	Austin Health	145 Studley Road	3084	Heidelberg
Australia	Hahn, Uwe	The Queen Elizabeth Hospital	28 Woodville Road	5011	Woodville
Australia	Johnston, Anna	Royal Hobart Hospital	48 Liverpool Street	7000	Hobart
Australia	Milliken, Samuel	St Vincent's Hospital	390 Victoria Street	2010	Darlinghurst
Australia	Rowlings, Philip	Calvary Mater Hospital	Cnr Edith & Platt Street	2298	Waratah
Australia	Schwarer, Anthony	Eastern Clinical Research Unit	5 Arnold Street	3128	Box Hill
Australia	Szer, Jeffrey	Royal Melbourne Hospital	Grattan Street	3050	Parkville
Australia	Szer, Jeffrey	Peter MacCallum Cancer Centre Ethics Committee	10 St Andrews Place	3002	East Melbourne
Belgium	Aoun, Mickael	Institut Jules Bordet	Boulevard de Waterloo 121	1000	Bruxelles
Belgium	Kerre, Tessa	UZ Gent	De Pintelaan 185	9000	Gent
Belgium	Maertens, Johan	UZ Leuven - Campus Gasthuisberg	Herestraat 49	3000	Leuven
Belgium	Schots, Henri	UZ Brussel	Laarbeeklaan 101	1090	Jette
Belgium	Selleslag, Dominik	AZ Sint-Jan Brugge - Oostende AV - Campus Sint-Jan	Ruddershove 10	8000	Brugge
Belgium	Theunissen, Koen	Jessa Ziekenhuis - Campus Virga Jesse	Stadsomvaart 11	3500	Hasselt
Belgium	Willems, Evelyne	Centre Hospitalier Universitaire de Liège	Domaine Universitaire du Sart Tilman	4000	Liege
Belgium	Zachee, Pierre	Ziekenhuisnetwerk Antwerpen - AZ Stuivenberg	Lange Beeldekensstraat 267	2060	Antwerpen
Bulgaria	Ganeva, Penka	CTH Sofia	6, Plovdivsko Pole St.	Not Defined	Sofia
Canada	Broady, Raewyn	Vancouver General Hospital	855 West 12th Avenue	V5Z 1M9	Vancouver
Canada	Cantin, Guy	CHU de Quebec - Hopital de l'Enfant-Jesus	1401, 18e Rue	G1J 1Z4	Quebec City
Canada	Comeau, Terrance	Saint John Regional Hospital	400 University Avenue	E2L 4L2	Saint John
Canada	Kuruvilla, John	Princess Margaret Hospital	610 University Avenue	M5G 2M9	Toronto
Canada	Olney, Harold	Centre Hospitalier de l'Université de Montréal (CHUM)	1051 Rue Sanguinet	H2X 3E4	Montréal
Canada	Sabry, Waleed	Saskatoon Cancer Centre	20 Campus Drive	S7N 4H4	Saskatoon
Czechia	Novak, Jan	Fakultni nemocnice Kralovske Vinohrady	Srobarova 50	100 34	Praha 10
Czechia	Papajik, Tomas	Fakultni nemocnice Olomouc	I.P.Pavlova 6	775 20	Olomouc
Czechia	Pohlreich, David	VFN Praha	U Nemocnice 2	128 08	Praha 2
Czechia	Zak, Pavel	FN Hradec Kralove	Sokolska 581	Not Defined	Hradec Kralove
Estonia	Loigom, Diana	North Estonia Medical Center	J. Sutiste tee 19	13419	Tallinn
Finland	Anttila, Veli-Jukka	Helsingin yliopistollinen keskussairaala	Haartmaninkatu 4	00029	Helsinki
Finland	Salmi, Tommi	Turun yliopistollinen keskussairaala	Hameentie 11	20520	Turku
Finland	Sinisalo, Marjatta	Tampereen yliopistollinen sairaala	Teiskontie 35	33520	Tampere
France	Bay, Jacques-Olivier	CHU Estaing	1 place Lucie Aubrac	63003	Clermont-Ferrand Cedex 1
France	Bouabdallah, Reda	CRLCC Paoli-Calmettes	232, boulevard Sainte Marguerite	13273	Marseille cedex 9
France	Bulabois, Claude-Eric	CHU de Grenoble - Hôpital Michallon	Boulevard de la Chantourne	38043	Grenoble cedex 9
France	Dupuis, Jehan	Hôpital Henri Mondor	51, avenue du Maréchal de Lattre de Tassigny	94010	Créteil cedex
France	Lepretre, Stephane	Centre Henri Becquerel	Rue d'Amiens	76038	Rouen cedex 1
France	Milpied, Noel	CHU de Bordeaux - Hôpital du Haut Lévêque	Avenue de Magellan	33604	Pessac cedex
France	Quittet, Philippe	CHRU de Montpellier - Hôpital Saint-Eloi	80, avenue Augustin Fliche	34295	Montpellier cedex 5
Germany	Brossart, Peter	Universitaetsklinikum Bonn	Sigmund-Freud-Str. 25	53127	Bonn
Germany	Egerer, Gerlinde	Universitaetsklinikum Heidelberg	Im Neuenheimer Feld 410	69120	Heidelberg
Germany	Guenther, Andreas	Universitaetsklinikum Schleswig-Holstein	Schittenhelmstr. 12	24105	Kiel
Germany	Heinz, Werner	Universitaetsklinikum Wuerzburg	Oberduerrbacher Str. 6	97080	Wuerzburg
Germany	Karthaus, Meinolf	Staedtisches Krankenhaus Muenchen	Sanatoriumsplatz 2	81545	Muenchen
Germany	Kiani, Alexander	Klinikum Bayreuth	Preuschwitzer Str. 101	95445	Bayreuth
Germany	Klein, Stefan	Universitaetsklinikum Mannheim	Theodor-Kutzer-Ufer 1-3	68167	Mannheim
Germany	Kofla, Grzegorz	Charite	Charitéplatz 1	10117	Berlin
Germany	Nusch, Arnd	Gem. Praxis Drs. Nusch und Kalhori, Fachärzte für Hämatologie und Onkologie	Friedrichstr. 311	42551	Velbert
Germany	Schwartz, Stefan	Charite-Universitaetsmedizin Berlin	Hindenburgdamm 30	12200	Berlin
Germany	Silling, Gerda	Universitaetsklinikum Muenster	Albert-Schweitzer-Campus 1	48149	Muenster
Germany	Staib, Peter	St. Antonius-Hospital	Dechant-Deckers-Str. 8	52249	Eschweiler
Germany	de Wit, Maike	Vivantes Klinikum Neukoelln	Rudower Str. 48	12351	Berlin
Greece	Anagnostopoulos, Achilles	G. Papanikolaou General Hospital of Thessaloniki	Exohi	57010	Thessaloniki
Greece	Anagnostopoulos, Nikolaos	General Hospital of Athens " G. Gennimatas"	154 Mesogion Ave.	11527	Athens
Greece	Angelopoulou, Maria	National and Kapodistrian University of Athens Hematology	Agiou Thoma str., 17	115 27	Athens
Greece	Apostolidis, Ioannis	General Hospital of Athens Evangelismos	45-47 Ipsilantou street	106 76	Athens
Greece	Karianakis, Georgios	Diagnosis and Therapy Centre "Hygeia", Bone Marrow Trar	Erythrou Stavrou Str. & Kifisias Av. 4, Marousi	151 23	Athens
Hong Kong	Lie, Albert Kwok-Wai	Queen Mary Hospital	102 Pokfulam Road	Not Defined	Hong Kong
Hong Kong	Yip, Sze-Fai	Tuen Mun Hospital	Tsing Chung Koon Road	Not Defined	Tuen Mun
Israel	Grisariu, Sigal	Hadassah Medical Center	Hadassah Medical Center	91120	Jerusalem
Israel	Zuckerman, Tsila	Rambam Health Care Campus	Bat-Galim	31096	Hafia
Italy	Castagna, Luca	Istituto Clinico Humanitas	Via Manzoni, 56	20089	Rozzano (MI)
Italy	Cellini, Claudia	Ospedale Santa Maria delle Croci	Viale Randi, 5	Not Defined	Ravenna
Italy	Cuneo, Antonio	Azienda Osp. Universitaria Arcispedale S. Anna	Via Aldo Moro, 8	44124	Cona (FE)
Italy	Gaidano, Gianluca	Azienda Sanitaria Ospedale Maggiore della Carità di Novara	Corso Mazzini, 18	28100	Novara
Italy	Lucchesi, Alessandro	Istituto Scientifico Romagnolo per lo Studio e la Cura dei T	Via Piero Maroncelli, 40	47014	Meldola (FC)
Italy	Michieli, Mariagrazia	Centro di Riferimento Oncologico IRCCS	Via Franco Gallini, 2	33081	Aviano (PN)
Italy	Tosi, Patrizia	Ospedale degli Infermi	Viale Settembrini, 2	47900	Rimini
Italy	Zaja, Francesco	Azienda Ospedaliero Universitaria S. Maria Misericordia	P.zza S. Maria Misericordia	33100	Udine
Japan	Choi, Ilseung	National Hospital Organization Kyushu Cancer Center	3-1-1, Notame, Minami-ku, Fukuoka-city	811-1395	Fukuoka
Japan	Chou, Takaaki	Niigata Cancer Center Hospital	2-15-3, Kawagishi-cho, Chuo-ku, Niigata-city	951-8566	Niigata
Japan	Hidaka, Michihiro	Kumamoto Medical Center	1-5, Ninomaru, Chuo-ku, Kumamoto-shi	860-0008	Kumamoto
Japan	Ikeda, Takashi	Shizuoka Cancer Center	1007, Shimonagakubo, Nagaizumi-cho, Sunto-gun	411-8777	Shizuoka

Japan	Ishikawa, Takayuki	Kobe City Medical Center General Hospital	2-1-1, Minatojimaminami-machi, Chuo-ku, Kobe-city	650-0047	Hyogo
Japan	Ito, Takuo	National Hospital Organization Kure Medical Center and Ch	3-1, Aoyama-cho, Kure-city	737-0023	Hiroshima
Japan	Kakihana, Kazuhiko	Tokyo Metropolitan Komagome Hospital	3-18-22, Honkomagome, Bunkyo-ku	113-8677	Tokyo
Japan	Matsumoto, Morio	Shibukawa Medical Center	383, Shiroi, Shibukawa-city	377-0280	Gunma
Japan	Shimomura, Takeshi	Hiroshima-Nishi Medical Center	4-1-1, Kuba, Ohtake-shi	739-0651	Hiroshima
Japan	Sunami, Kazutaka	Okayama Medical Center	1711-1, Tamasu, Kita-ku, Okayama-city	701-1192	Okayama
Japan	Tanimoto, Mitsune	Okayama University Hospital	2-5-1, Shikata-cho, Kita-ku, Okayama-city	700-8558	Okayama
Japan	Yoshida, Shinichiro	National Hospital Organization Nagasaki Medical Center	2-1001-1, Kubara, Omura-city	856-8562	Nagasaki
Korea, Republic of	Cheong, June-Won	Yonsei University College of Medicine. Severance Hospital	250 Seongsanno,Seodaemun-gu	120-752	Seoul
Korea, Republic of	Eom, HyeonSeok	National Cancer Center	#809 Madoo-1dong, Ilsandong-gu, Goyang-si	410-769	Kyunggi-do
Korea, Republic of	Kim, SeokJin	Samsung Medical Center	50 Ilwon-Dong Gangnam-Gu	135-710	Seoul
Korea, Republic of	Kwak, Jae-Yong	Chonbuk National University Hospital,	634-18, KeumAm-Dong, DukJin-Gu,	561-712	Jeonju
Korea, Republic of	Lee, Dong-Gun	Seoul St. Mary's Hospital	222 Banpo-Daero, Seocho-Gu, Seoul 137-701, Korea	137-701	Seoul
Korea, Republic of	Lee, Jae Hoon	Gachon University Gil Hospital	1198 Kuwol-dong, Namdong-Gu	405-760	Incheon
Korea, Republic of	Lee, Je-Jung	ChonnamNational University Hwasun Hospital	160 Ilshimri,Hwasuneup	519-809	Jellanamdo
Korea, Republic of	Sohn, Sang Kyun	KyungPook National University Hospital	130 Dongdeok-ro, Jung-gu	700-721	Daegu
Korea, Republic of	Yoon, Sung soo	Seoul National University Hospital	28 Yongon-dong, Chongno-gu	110-744	Seoul
Malaysia	Tan, Sen Mui	Hospital Ampang	Jalan Mewah Utara, Pandanmewah	68000 Ampang	Selangor
Malaysia	Wahid, Fadilah	Universiti Kebangsaan Malaysia Medical Center	Jalan Yaacob Latif, Bandar Tun Razak, Cheras	56000	Kuala Lumpur
Netherlands	Marijt, Willem A.F.	Leids UMC	Albinusdreef 2	2333 ZA	LEIDEN
New Zealand	Berkahn, Leanne	Auckland City Hospital	Park Road	1003	Grafton
New Zealand	Butler, Andrew	Canterbury District Health Board	Corner Tuam Street and Hagley Avenue	8011	Christchurch
New Zealand	Carter, John	Wellington Hospital	Riddiford Street	6021	Wellington
Panama	Quiel, Dimas	Complejo Hospitalario Dr. Arnulfo Arias Madrid	Vía Simón Bolívar (Transístima)	Not Defined	Panama
Poland	Giebel, Sebastian	Centrum Onkologii-Instytut im. Marii Sklodowskiej-Curie-Oc	ul. Wybrzeze Armii Krajowej 15	44-101	Gliwice
Poland	Halaburda, Kazimierz	Instytut Hematologii i Transfuzjologii	ul. Indiry Gandhi 14	02-776	Warszawa
Poland	Piatkowska- Jakubas, Beata	Malopolskie Centrum Medyczne	Ul Rejtana 2	30510	Krakow
Romania	Benedek, Erzsebet	SPITALUL CLINIC JUDETEAN DE URGENTA TÎRGU-MURES,	Str. Revolutiei nr.35	540042	Tirgu Mures
Romania	Lupu, Anca Roxana	SPITALUL CLINIC COLTEA, Clinica de Hematologie	Bld. I.C.Bratianu nr.1	030171	Bucharest
Romania	Varady, Zsofia	INSTITUTUL CLINIC FUNDENI - Centrul de Hematologie si	Sos. Fundeni nr.258, Sector 2	022328	Bucharest
Russian Federation	Kryuchkova, Irina	Research institute of clinical immunology	14 Yadrintsevskaya str.	630099	Novosibirsk
Russian Federation	Kuvshinov, Aleksey	Russian Hematology and Transfusiology Research Center	16, 2nd Sovetskaya str.	191024	St'Petersburg
Russian Federation	Myasnikov, Alexandr	Republican Hospital nom Baranov	3, Pirogov street	185019	Petrozavodsk
Russian Federation	Rukavitsyn, Oleg	Burdenko Main Military Clinical Hospital	3, Gospitalnaya sq.	105 229	Moscow
Russian Federation	Shnayder, Tatiana	Leningradskaya regional Clinical Hospital	Lunacharskogo, 45	194291	St.-Petersburg
Russian Federation	Tyurina, Natalya	Moscow Oncology Research Institute n.a. Herzen	3, 2nd Botkinskyi dr.	125101	Moscow
Russian Federation	Uvarov, Mikhail	City Clinical Hospital # 31	Prospekt Dinamo	197110	St.Petersburg
South Africa	Cohen, Graham	Little Company of Mary Hospital	50 Totius Street	0181	Groenkloof
South Africa	McDonald, Andrew	Albert Alberts Stem Cell Transplant Centre	c/o Netcare and Garsfontein Road	0001	Moreleta Park, Pretoria
South Africa	Ruff, Paul	Wits Donald Gordon Clinical Trial Site	18 Eton Road	2193	Parktown
South Africa	du Toit, John	Cape Haematology and Bone Marrow Transplant Unit	Burnham Road	Not Defined	Plumstead
Spain	Alonso Alonso, Aránzazu	Hospital Quirón Madrid	c/ Diego de Velázquez, 1	28223	Pozuelo de Alarcón/Madrid
Spain	Aláez Usón, María de la Concepción	CLINICA MONCLOA	Avda. de Valladolid, 83	Not Defined	Madrid
Spain	Campins Martí, Magda	Hospital Universitario Valle de Hebron	Paseo De Valle De Hebron 119 - 129	08035	Barcelona
Spain	Deben Ariznavarreta, Guillermo	Hospital Universitario a Coruña	Calle Xubias de Arriba Nº84	15006	La Coruña
Spain	Esquirol Sanfeliu, Albert	Hospital Santa Creu i Sant Pau	Avda. San Antoni Maria Claret, 167	08025	Barcelona
Spain	Ferra Coll, Christelle	Hospital Germans Trias i Pujol	Crtra. Canyet s/n	08916	Badalona/Barcelona
Spain	Gayoso Cruz, Jorge	Hospital Gergorio Marañón	C/ Maiquez, 7	28009	Madrid
Spain	González Rodríguez, Ana Pilar	Hospital Central de Asturias	C/Celestino Villamil, s/n	33006	Oviedo
Spain	Heras Fernando, Inmaculada	Hospital General Universitario J.M. Morales Meseguer	Marqués de los Vélez, s/n	30008	Murcia
Spain	Jarque, Isidro	Hospital Universitario La Fe	Bulevar sur s/n.Carretera de Malilla.	46026	Valencia
Spain	Krsnik Castelló, Isabel	Hospital Puerta de Hierro	C/ Manuel de Falla, 1	28222	Majadahonda (Madrid)
Spain	Llamas Sillero, Pilar	Fundación Jiménez Díaz	Av. Reyes Católicos, 2	28040	Madrid
Spain	López Jiménez, Javier	Hospital Ramón y Cajal	Ctra.de Colmenar Viejo km.9,1	28034	Madrid
Spain	Martínez Muñoz, Carmen	Hospital Clinic i Provincial	C/ Villarroel, 170	08036	Barcelona
Spain	Monserrat Coll, Jorge	Hospital Virgen de la Arrixaca	Ctra. Madrid-Cartagena, s/n	30120	Murcia (El Palmar)
Spain	Pascual Cascón, María Jesús	Hospital Carlos Haya	Avda. Carlos Haya s/n	29010	Malaga
Spain	Perez de Oteyza, Jaime	Centro Oncológico Integral Clara Campal	C/ Oña, 10	28050	Madrid
Spain	Polo Zarzuela, Marta	Hospital Clínico San Carlos	c/ Dr. Martín Lagos s/nº	28040	Madrid
Spain	Riaza Grau, Rosalía	Hospital Severo Ochoa	Avda. Orellana, s/n	28911	Madrid
Spain	Solano Vercet, Carlos	Hospital Clínico de Valencia	Avd. Blasco Ibáñez, 17	46010	Valencia
Spain	Vallejo Llamas, Carlos	Hospital de Donosti	Paseo Dr. Beguiristain, s/n	20014	San Sebastián
Spain	Yáñez San Segundo, Lucrecia	Hospital Marqés de Valdecilla	Avda. Marqués de Valdecilla, 25	39008	Santander
Spain	de Oña Navarrete, Raquel	MD Anderson	C/ Arturo Soria, 270	28033	Madrid
Spain	de la Serna Torroba, Javier	12 de Octubre	Avda. de Córdoba s/n	28041	Madrid
Spain	de las Heras Rodríguez, Natalia	Hospital de León	Travesia de los Altos del Castillo s/n	24008	León
Taiwan	Kuo, Ching-Yuan	Chang Gung Memorial Hospital- Kaoshiung	No. 123, Ta-Pei Road, Niao-Sung Hsiang,	833	Kaohsiung
Taiwan	Teng, Chieh-Lin	Taichung Veterans General Hospital	1650 Taiwan Boulevard Sec.4	40705	Taichung
Taiwan	Wang, Po-Nan	Chang Gung Memorial Hospital	5. Fu-Hsing Street, Kuei Shan Hsiang, Taoyuan Hsien 333, Taiwan.	333	Taoyuan Hsien
Taiwan	Yeh, Su-Peng	China Medical University Hosital	No.2, Yuh-Der Road	404	Taichung
Turkey	Arat, Mutlu	Istanbul Bilim University Medical Fac.	Abide-i Hurriyet Cad. No: 164	34481	Istanbul
Turkey	Barista, Ibrahim	Hacettepe University Medical Faculty	Sihhiye	06100	Ankara
Turkey	Beksac, Meral	Ankara University	Ankara	Not Defined	Ankara
Turkey	Vural, Filiz	Ege University SoM	Bornova	Not Defined	Izmir
Turkey	Yegin, Arzu	Gazi University Medical Faculty	Besevler	06500	Ankara

United Kingdom	Bailey, James	Castle Hill Hospital	Castle Road	HU16 5JQ	Cottingham
United Kingdom	Blesing, Norbert	The Great Western Hospital	Marlborough Road	SN3 6BB	Swindon
United Kingdom	Bloor, Adrian	The Christie NHS Foundation Trust	Wilmslow Road	M20 4BX	Manchester
United Kingdom	Cook, Gordon	St James University Hospital	Beckett Street	LS9 7TF	Leeds
United Kingdom	Murphy, John	Monklands Hospital	Monkscourt Avenue	ML6 0JS	Airdrie
United Kingdom	Peniket, Andrew	Churchill Hospital	Old Road	OX3 7LE	Headington, Oxford
United Kingdom	Rocci, Alberto	Manchester Royal Infirmary	Oxford Road	M13 9WL	Manchester
United Kingdom	Walewska, Renata	Royal Bournemouth Hospital	Castle Lane East	BH7 7DW	Bournemouth
United States	Abhyankar, Sunil	University of Kansas Cancer Center	2330 Shawnee Mission Parkway	66205	Westwood
United States	Andreadis, Charalambos (Babis)	University of California Medical Center	400 Parnassus Ave	94143	San Francisco
United States	Boeckh, Michael	Fred Hutchinson Cancer Research Center	1100 Fairview Avenue	98109-1024	Seattle
United States	Buadi, Francis	Mayo Clinic	200 1st Street S W	55905	Rochester
United States	Chandrasekar, Pranatharthi	Karmanos Cancer Institute	4160 John R. - Suite 711	48201	Detroit
United States	Chauncey, Thomas	Veterans Administration Puget Sound Health Care System	1660 South Columbian Way	98108	Seattle
United States	Dadwal, Sanjeet	City of Hope National Medical Center	1500 East Duarte Road	91010	Duarte
United States	Flomenberg, Phyllis	Thomas Jefferson University	1015 Chestnut Street	19107	Philadelphia
United States	Gentile, Teresa	SUNY Upstate Medical University	750 E. Adams Street	13210	Syracuse
United States	Greenberg, Richard	University of Kentucky	800 Rose Street	40536	Lexington
United States	Gutman, Jonathan	University of Colorado Cancer Center	1665 Aurora Court	80045	Aurora
United States	Hall, Matthew	Marshfield Clinic	1000 N. Oak Avenue	54449	Marshfield
United States	Issa, Nicolas	Brigham and Women's Hosptial	75 Francis Street	02115	Boston
United States	Issa, Nicolas	Massachusetts General Hospital	32 Fruit Street	02114	Boston
United States	Klein, Andreas	Tufts Medical Center	800 Washington St	02111	Boston
United States	Mossad, Sherif	Cleveland Clinic Foundation	9500 Euclid Avenue	44195	Cleveland
United States	Rowley, Scott	Hackensack University Medical Center	92 Second Street, Suite 119	07601	Hackensack
United States	Satlin, Michael	Weill Medical College of Cornell University	1300 York Avenue	10021	New York
United States	Shea, Thomas	University of North Carolina at Chapel Hill	101 Manning Drive	27599	Chapel Hill
United States	Stadtmauer, Edward	University of Pennsylvania	3400 Civic Center Blvd.	19104	Philadelphia
United States	Sullivan, Keith	Duke Medicine	2400 Pratt St	27705	Durham
United States	Vance, Estil	Sammons Cancer Center	3410 Worth Street	75246	Dallas
United States	Young, Jo-Anne	University of Minnesota	420 Delaware Street	55455	Minnesota