Safety and Effectiveness of Live Zoster Vaccine in Anti-Tumor Necrosis Factor (TNF) Users (VERVE Trial)

Study Protocol & Statistical Analysis Plan

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The Safety and Effectiveness of the VaricElla zosteR VaccinE (VERVE) in Anti-TNF Users

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DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all sub-investigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UAB.

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Investigator:

_____ _____

Printed Name Date/Signature

1 Background and Rationale

1.1 Herpes Zoster and Zoster Vaccine

The reactivation of varicella zoster virus (herpes zoster [HZ] or "shingles") is of substantial public health concern. Its predilection for the elderly and the immunosuppressed make it an important cause of morbidity, resulting in pain, depression, and long-term disability in the form of post-herpetic neuralgia (PHN), encephalitis, ophthalmic disease with permanent vision loss, and neurologic manifestations including Ramsay Hunt syndrome. Further, the ability of HZ to cause disseminated complications and death in immunosuppressed individuals is well-documented.[1-3] In the United States, HZ incidence rates rise with age and range between 4 to 11 per 1,000 patient-years (PYs) in patients aged 50 and 80 respectively, with rates highest in women.[1-4]

Recently, a live-attenuated vaccine to prevent HZ (*Zostavax®,* Merck) was developed and approved for use in the general population aged 50 years or older, regardless of previous HZ or varicella history. In the Shingles Prevention Study (SPS), a pivotal study of 38,456 adults aged ≥ 60 years led by Dr. Michael Oxman, the vaccine reduced the burden of illness (BOI) and the incidence of HZ and PHN 66.5%. In a more recent trial of adults aged 50-59, the vaccine was shown to confer even greater protection, with efficacy of 70% at preventing HZ.[5-6] These studies, however, could not evaluate the safety and effectiveness of this vaccine in patients with rheumatoid arthritis (RA) or other key high risk groups for whom the vaccine might have substantial benefit because such patients were excluded from the trial, limiting its generalizability.

1.2 Risk of Herpes Zoster in Patients with Rheumatoid Arthritis and Recommendations regarding Vaccination with the Live Zoster Vaccine

Patients with rheumatoid arthritis (RA) are at an approximately 2 fold higher risk of HZ compared to the general population, making the prevention of HZ in this population a high priority. This increased risk is likely due in part to the underlying disease state of RA, but also in part may be due to the immunosuppressive therapies (e.g. glucocorticoids) employed against the disease.[7-8] Given the increased risk of this disease in RA patients and its potential for long-term morbidity, the availability of an effective vaccine can improve the health-quality of the 2+ million RA patients in the United States. However to date, few RA patients in the United States have received this vaccine (< 5%, based upon national data) despite its recommendation, likely due to safety concerns associated with the administration of a live attenuated vaccine to patients using immunosuppressive medications.[9]

In 2008, guidelines from the CDCs Advisory Committee on Immunization Practices (ACIP) recommended that patients who use methotrexate at < 0.4 mg/kg/week (e.g. <= 25 mg/week for a 70 kg individual) or low to moderate doses of corticosteroids (up to 20 mg/day prednisone) could receive this vaccination safely,[4] despite a lack of safety and efficacy data for such individuals. In contrast, although with a similar void in data, theoretical concerns regarding the safety of live vaccine use in patients using biologic therapies such as anti-TNF agents have resulted in an ACIP recommendation contraindicating the vaccine in patients receiving anti-TNF or other biologics. This recommendation was based solely upon expert opinion, as the vaccine (Zostavax®) had not been studied specifically in such individuals and there was a near-complete absence of experimental or observational data. The American College of Rheumatology (ACR) endorsed this contraindication in its ACR 2012 recommendations for biologic and non-biologic disease modifying anti-rheumatic drug (DMARD) use in RA patients (developed by several of the study investigators including Drs. Curtis, Winthrop, and Saag); however this endorsement echoed the ACIP recommendations and was not data-driven.[10] Currently, it is unknown if Zostavax® represents a safety risk for patients using biologic therapy. The lack of information concerning this question presents a major gap in the clinical care of patients with RA and poses a barrier to the prevention of the common and sometimes debilitating manifestations and complications of HZ.

1.3 Safety of the Zoster Vaccine in Patients using Anti-TNF Therapies

1.3.1 Potential Safety Concerns for Patients with Autoimmune Diseases

Despite the demonstrated efficacy and safety of the zoster vaccine observed in non-RA patients, there are no prospective data critically examining the efficacy or safety of HZ vaccination in RA patients. The zoster vaccine was not administered to immunosuppressed participants in the large Shingles Prevention Study (SPS)[5]; potential participants with RA and other autoimmune diseases receiving immunosuppressive or immunomodulating agents including glucocorticoids and biologic and non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) were excluded from the pivotal trials of the vaccine. However, several lines of evidence suggest the possibility that this vaccine might be safe when given to patients using biologic therapy. First, the pivotal SPS of more than 38,000 patients aged 60+ did not identify safety concerns of the vaccine, even in very elderly individuals, including those with little evidence of remaining varicella zoster virus (VZV) specific cell mediated immunity (CMI).[11-12] In addition, live varicella vaccine has been safely administered to both children and adults with HIV infection.[3-4, 6, 11-14] Further, there is observational evidence to suggest that patients who use anti-TNF therapy are not at higher risk to develop HZ.[15-16] Additionally, for patients who do

develop HZ, they do not appear to be at higher risk of HZ complications, including cutaneous or visceral dissemination. We recently examined this question within a cohort of over 30,000 anti-TNF users within the US and found no increased risk of HZ in patients who start anti-TNF therapy as compared to those starting non-biologic DMARDs.[16] Although the data are not consistent in this regard,[8] other studies have also failed to demonstrate a significant risk for HZ associated with some anti-TNF therapies.[15]

1.3.2 Safety of Zostavax® in the General Population

The efficacy and safety of zoster vaccine in the general population were examined in the two large clinical trials discussed above, first in those >60 years of age, the SPS, which was followed by a trial of immunocompetent individuals 50-59 years of age.[2, 4] In both trials, the primary risk window for evaluating vaccine related complications due to live virus inoculation was 42 days post-vaccination. In the SPS study, low and similar rates of serious adverse events (SAEs) were observed in both the vaccinated and placebo group (1.4% in both); moreover, significantly fewer confirmed HZ cases occurred in the vaccine group (n=7) as compared to placebo (n=24) [$p < 0.05$] in the 42 days after vaccination.[5] Among those 50 to 59 years of age, the findings were similar, although SAE event rates were even lower in both groups (0.6% in each group) during this 42-day window.[17]

Post-licensure, large observational studies have reported similar effective and safety as reported by the clinical trial programs. In one large observational study conducted among 75,761 vaccinated and 227,283 unvaccinated immunocompetent community dwelling individuals 60 years and older, Zostavax® was associated with a 55% reduction in HZ incidence.[18] In addition, in a separate safety analysis of 193,083 vaccinated individuals 50 years and older, the vaccine was not associated with an increased risk of adverse events within the first 42 days following vaccination except for localized non-serious self-limited injection site reactions.[19] Taken together, these data support the safety of Zostavax® among older persons in the community, with a low SAE rate that does not differ from placebo.

1.3.3 Zostavax® Safety among Biologic-exposed Patients with Autoimmune Diseases

We conducted a retrospective cohort study to examine the safety and effectiveness of zoster vaccine among Medicare beneficiaries diagnosed with RA or other immune-mediated diseases (psoriatic arthritis, psoriasis, ankylosing spondylitis, or inflammatory bowel disease). We used 100% Medicare data from January 1, 2006 through December 31, 2009 and required eligible patients to be 60 years and older with autoimmune diseases and to have fee for service plus outpatient prescription drug coverage.[20] A total of 463,115 patients were included in the

analysis; their mean ± standard deviation (SD) age was 74 ± 8 years; 72.3% were women, 86.3% were Caucasians and 18,931 patients received the zoster vaccine. Among the 463,115 patients included in the analysis, only 4% were vaccinated with the zoster vaccine[21]. The low vaccination rate in these Medicare patients is consistent with a similarly low rate observed in another study we conducted in RA patients using national data from a commercial health plan (Aetna).[6, 9]

In the Medicare population, we identified 663 patients who were exposed to a biologic agent, including 551 to an anti-TNF biologic agent, at the time of, or within 42 days after, vaccination. Among these patients, none developed HZ or any infection complications or syndromes (e.g. hospitalized meningitis or encephalitis) suggestive of VZV disease within the 42 days following vaccination. Among vaccinated patients, one developed presumed primary VZV infection within the 42-day risk window, but the patient was not exposed to any biologic during the 6 months preceding or after vaccination. Beyond 42 days after vaccination until study-end, 138 HZ cases were observed during 20,639 PYs (crude incidence rate 6.7 cases per 1,000 PYs), which indicated a 41% reduction in the crude rate of HZ compared to unvaccinated person-time (crude incidence rate 11.6 cases per 1,000 PYs). In terms of absolute risk reduction, the HZ vaccine reduced HZ risk by 7.0 cases per 1,000 person-years. This benefit was comparable to and numerically greater than the corresponding risk difference of 5.7 cases observed in the SPS. Adjusting for demographics, type of immune-mediated disease, health care utilization, and exposure to biologic and non-biologic DMARDs and oral glucocorticoids, zoster vaccine was associated with a 39% relative reduction in the rate of HZ infection (adjusted hazard ratio 0.61 [95% CI; 0.52-0.71]). The receipt of the zoster vaccine was effective and associated with similar absolute reductions in HZ risk and subsequent post-herpetic neuralgia as that observed in the SPS. The associated number needed to treat (NNT) (i.e. vaccinate) to prevent a HZ case was 142 among RA patients and was numerically lower than the NNT of 175 seen in the SPS among the older individuals in the general population who are currently recommended by the CDC to receive the vaccine. Thus, based upon a more favorable absolute risk reduction for the zoster vaccine and a lower associated NNT in the RA population, the need to vaccinate these older patients with RA is compelling. However, critically important but unanswered safety questions are an impediment to optimizing quality of care for RA patients through use of the vaccine. While our previous publication in JAMA suggested that the zoster vaccine was safe even among anti-TNF users, the analysis was hindered by limitations common to administrative data. Moreover, it was not definitive as to warrant changing clinical practice or to adequately reassure patients and clinicians regarding safety. Although it might be possible to discontinue biologic

treatments for at least 1-2 months (to facilitate drug washout), vaccinate and then restart biologic therapy approximately one month following vaccination, our findings suggest that this strategy is rarely employed,. This may be due to concern regarding a flare in RA disease while off biologic therapy for the prolonged time-period necessary to vaccinate, making this practice unacceptable to many patients and their physicians. Together, these data suggest that in addition to usual barriers to adult vaccination in the general population, additional safety concerns likely further discourage zoster vaccine use for RA patients using biologics.

1.3.4 The VaricElla zosteR VaccinE (VERVE) Study Rationale

Given the 1) widespread use of anti-TNF therapy, 2) the increased risk of HZ in RA patients, 3) evidence that zoster vaccination occurs infrequently among RA patients; and 4) preliminary observational data suggesting that the use of zoster vaccine may be safe and effective in RA patients, it is of key public health importance to prospectively evaluate the safety and effectiveness of Zostavax® in RA patients using anti-TNF therapy.

2 Study Objectives

To conduct a large, randomized, double-blind, placebo-controlled trial to evaluate the zoster vaccine (*Zostavax®*, Merck) in 1,000 patients using anti-TNF therapies to meet three specific objectives:

2.1 Primary Objectives and endpoint

- To evaluate vaccine immunogenicity by measuring VZV-specific T cell responses (correlates of HZ immunoprotection) and VZV glycoprotein-specific (gp-specific) antibody titers (used as surrogate outcomes in the prior SPS trial).We hypothesize that patients using anti-TNF therapies who receive the live zoster vaccine will be able to achieve a greater increase in the VZV-specific T cell response measured 6 weeks post vaccination compared to patients using anti-TNF therapies receiving placebo. Patients who have a 6 week visit (with labs) have sufficient data to be considered complete for the primary lab-based outcome.

2.2 Secondary Objectives and endpoints

- To estimate the clinical effectiveness of the HZ vaccine in reducing longer-term HZ risk. Incident HZ cases occurring following vaccination will be ascertained among enrollees in Medicare and/or large commercial health plans (e.g. WellPoint, comprising Blue Cross / Blue Shield plans in 14 U.S. states) using a novel linkage to administrative health plan data. We will examine longer-term reduction in risk for herpes zoster and the potential for

decreased vaccine effectiveness over time to prevent HZ, which might suggest waning immunity and the need for re-vaccination. This outcome will be ascertained using administrative claims data among the majority of VERVE participants who are linkable to the health plan data sources available to the trial, albeit with a recognition that the amount of follow-up time will be modest, and conditional on the availability of patients being linkable to such data.

- To estimate vaccine safety using a composite outcome of all serious adverse events (SAEs) AND non-serious vaccine-strain VZV events within 42 days of vaccination, the relevant safety window as used in the SPS. Serious adverse events of interest will include all serious adverse events that satisfy the FDA-accepted definition of SAEs (results in death, life threatening, results in or prolongs hospitalization, etc.). The hypothesis to be tested by the trial is that vaccination with Zostavax® is non-inferior to placebo injection in the cumulative incidence of the composite safety outcome occurring within 42 days after vaccination. We will also examine vaccine tolerability including injection site reactions and flares in RA disease activity within 6 weeks following vaccination. RA disease activity will be measured using the clinical disease activity index (CDAI) and the Rapid Assessment of Patient Data (RAPID3).

3 Study Design

3.1 Study Overview

The VaricElla zosteR VaccinE (VERVE) trial is a 2-arm, double-blinded, multicenter randomized pragmatic clinical trial designed to determine whether the currently licensed zoster vaccine is safe and effective in patients with inflammatory arthritis and other diseases requiring use of anti-TNF therapies. We propose to recruit 1,000 patients 50 years or older currently using any anti-TNF therapy from clinical practices and randomize these participants (1:1) to receive either the HZ vaccine or placebo (saline).Study procedures will be facilitated on site after site has received Institutional Review Board approval for this study.

The study will be conducted in two consecutive phases; the trial design described below had extensive input from the VERVE steering committee during the tenure of the planning grant period. It also conforms to the recommendations made by the FDA committee that responded to the VERVE investigators' IND application. This FDA conference with the study team was held in February 2012, and the subsequent written guidance from FDA was incorporated into the trial design under approved IND #15202.

All patients will have two in-clinic visits, one at screening/randomization (a single visit) and again at 6 weeks follow-up. Blood samples will be drawn at these visits and additional safety data from at-home patient diaries will be collected from these participants. Participants will be contacted by telephone three- five (3-5) days after receiving either Zostavax® or Placebo and then every week until their 6 weeks in-office follow up visit to remind participants to complete the vaccine report card (diary), to check for early post-vaccination AEs and as a reminder to notify their study contact for changes in health status that might indicate VZV disease (such as rash). All participants will have a 6 month telephone contact to assess for post-vaccination AEs. Patients that received the Zostavax injection and agree will have a follow-up visit at 1 year post randomization for blood draw and clinical data collection. Conditional on future funding, patients will be contacted annually for up to ten years. The main study is 6 months in duration. Everything beyond the 6 month telephone contact is considered the extension phase of the study and is relevant only for intervention patients and not placebo-treated patients.

For all participants who are enrolled in a health plan with data that can be linked to VERVE (e.g. Medicare), effectiveness follow-up will be assessed after randomization and will rely on linked administrative data (medical, pharmacy claims). Patients will be consented for this linkage and required to sign a VERVE study specific authorization form to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information, including linkage with health plan data. In addition to the VERVE study specific authorization form, sites may have a site specific form if required by a local institutional review board, but it will not replace the required VERVE form. The VERVE study specific authorization form has been reviewed and approved for use by the University of Alabama at Birmingham Institutional Review Board under the VERVE Coordinating Center protocol. The duration of follow-up in health plan data is expected to be at least one year. Conditional on future funding, more extended follow-up is anticipated using this method, up through ten years.

3.2 Data Collection for Phase I and Phase II

Phase Ia and Phase Ib

Initially, Phase Ia will recruit patients who are being treated with an anti-TNF therapy with or without DMARDs, and who test positive for Varicella IgG from the University of Alabama at Birmingham (UAB), Oregon Health and Science University (OHSU) rheumatology clinics, and other select clinical sites if needed. Varicella IgG status must be known at or prior to randomization and may be used as long as it is verified as positive within three years prior to randomization. For Phase Ia patients and consistent with the FDA guidance provided during our

pre-IND meetings with FDA, any patients having received any parenteral or oral corticosteroids in the last 30 days will be excluded. Following randomization, data on the occurrence of rash or other local or systemic symptoms suggestive of VZV infection from day 0 to day 42 following vaccination will be collected (see below). These data will be collected at the 6-week, in-person follow-up visit, as well as via at-home patient diaries (vaccine patient report card) filled out during this 42 day interval. To facilitate this data collection, these Phase Ia participants will be provided with an at-home paper diary to record AEs. The diary will collect information about injection site reactions, and other AEs using methods similar to the SPS trial.[5] Subjects will also be asked to provide information regarding RA disease activity and flare. This diary will be reviewed at the 6 week in-person visit. Additionally, patients will be prompted at baseline to promptly report any AEs or SAEs that occur within the first 42 days to their study physician as soon as they may occur. They will also receive once weekly phone calls from study site staff to prompt for information regarding AEs and SAEs of interest. Any symptom suggestive of an SAE or a VZV event (e.g. new painful skin rash, constitutional symptoms such as fever, other symptoms in the skin and subcutaneous tissue MEDRA category) will trigger the need for the patient to return for an in-person safety visit.

Assuming that no serious safety concerns are identified and conditional on FDA, DSMB, and IRB approval, Phase I will continue to Phase Ib and recruit patients between UAB, OHSU and select clinical sites For these additional patients, confirmation of varicella IgG status must be known, as described above. However, the prohibition against use of recent or current glucocorticoid therapy will be dropped, and patients may be included if they have received prednisone-equivalent doses of up to 10 mg per day, as long as the dose has been stable for the last 30 days. The initial expectation is that Phase 1a will enroll approximately 100 patients, and phase 1b will enroll approximately 150 additional patients to yield a total of 250 patients in Phase 1 overall. However, these specific numbers are conditional on guidance from the DSMB and the FDA; and the trial may be advanced to a subsequent phase earlier conditional on approval from the DSMB, FDA and IRB.

Phase II

The second phase of the trial (Phase II) will enroll to a total of 1000 patients from additional academic and community sites. The eligibility criteria are the same with those from the end of the Phase I study, but with the removal of the positive VZV test criteria. Safety data that will support the primary outcome of the trial will be collected via a scheduled in-clinic visit 6 weeks after vaccination and a 6 month phone call. Patients will also be instructed to report any AEs

suggestive of a VZV event and any SAEs that occur within the first 42 days promptly to their study physician and return for an in-person visit as soon as they may occur.

3.3 Storage of Specimens for Future Use

As part of this study, blood specimens collected from participants will be stored for future research on arthritis, other auto-immune related diseases, inflammation, and varicella. The purpose is to make the specimens available for future research that is not yet planned. The future research may be conducted by Jeffrey Curtis, MD from the University of Alabama at Birmingham or by other researchers that obtain Institutional Review Board (IRB) approval for their research. Specimens will be stored in a central location at the UAB VERVE Coordinating Center Biorepository. Storing specimens is not an optional part with respect to participation within the study. However, participants have the option to choose whether or not they would like their specimens to be used for possible future research. Participants will indicate on the informed consent document whether or not they agree to allow specimens to be kept and used for future research involving other diseases.

The specimens stored will be labeled with a unique de-identified study subject number. Researchers are required to protect participant's privacy and keep information private to the extent permitted by law. Clinical data associated with the specimens will be entered to the online electronic data capture system, Velos, used for the trial. All data captured will be secured and locked on a password protected computer database.

The results of tests performed on stored samples for future research will not be given to participants. There will be no benefit for participants from the storage of specimens. However, the specimens obtained from participants in this research may help in the development of a future commercial product. There are no plans to provide financial compensation if this occurs.

Participants can request by written letter to withdraw from the study and have their unused research specimens destroyed. Participants will submit their request in writing to the UAB VERVE Study, Attn: Dr. Jeffrey R Curtis via fax: (205) 934-1301 or mail: 1720 2nd Avenue South, AB 470, Birmingham, AL 35294-0104. If participants do not submit a written request to withdraw from the study, specimens will be stored indefinitely or until used.

3.4 Study population

3.4.1 Inclusion Criteria

Patients must meet all of the inclusion criteria

- Must be 50 years of age or older
- Must be currently treated with an anti-TNF therapy** at the time of study drug administration, allowing for small deviations in dosing frequency and logistic feasibility (e.g. study visits to occur on a week day). Date of previous dose of medication is required. Specifically, meets one of the following:
  Etanercept dose within 9 days (1 week + 2 days)
  Adalimumab dose within 16 days (2 weeks + 2 days)
  Certolizumab SC dose within 16 to 32 days depending on frequency schedule (2 weeks + 2 days, or 4 weeks and 4 days)
  Golimumab SC dose within 32 days (4 weeks + 4 days)
  Golimumab IV dose within 64 days (9 weeks + 1 day)
  Infliximab IV dose within last 64 days (9 weeks + 1 day)
  **** any form of biosimilar for the above listed anti-TNF medications is acceptable**
- Diagnosis of RA or another inflammatory arthritis (Phase Ia); or RA, another inflammatory arthritis, or other inflammatory condition (e.g. psoriasis) requiring use of anti-TNF therapy (Phase Ib and II)
- Phase I subjects must test positive for VZV IgG
- Subjects should have a self-reported history of prior varicella infection (i.e. chicken pox) or long-term residence (>30 years) in the continental US.
- Phase Ia subjects must not have received any oral or systemic glucocorticoids within 30 days prior to vaccination. Intra-articular glucocorticoid injections and inhaled glucocorticoids within the previous 30 days are acceptable.
- Subjects should be on stable doses of all biologic and non-biologic DMARDs for a minimum of 30 days prior to vaccination.
- Eligible women must be post-menopausal (> 1 year since last menstrual period) or have a surgical history of bilateral oophorectomy or hysterectomy.
- Subjects should be ambulatory, community dwelling and capable of giving informed consent.

3.4.2 Exclusion Criteria

Patients will be excluded if they meet any of the following exclusion criteria

- Documented VZV negative result
- Prior use of the zoster vaccine (Zostavax®, Merck)

- Glucocorticoids at a prednisone-equivalent daily dose > 10mg/day (for Phase 1b and Phase II participants; all systemic glucocorticoid use is prohibited for Phase Ia patients)
- Any known contraindication to Zostavax® vaccine, including allergy or sensitivity to gelatin or any other vaccine component
- Known HIV/AIDS
- Currently receiving radiation or chemotherapy for any type of malignancy
- Any current use (within the last 30 days) of acyclovir, valacyclovir, famciclovir, or foscarnet
- Receipt of any other immunizations within one month before study vaccination (2 weeks in the case of inactivated influenza vaccines or other non-replicating immunization products [e.g., dT, pneumococcal vaccine, hepatitis A vaccine, hepatitis B vaccine]), or scheduled within 6 weeks after recruitment.
- Active infection or inter-current illness (e.g., urinary tract infection, influenza)
- Participated in an investigational study within 1 month prior to study entry
- Active drug or alcohol use, dependence, or any other reason that, in the opinion of the site investigator, would interfere with the study
- Significant underlying illness that would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 3 years)
- Any other reason that, in the opinion of the site investigator, would interfere with required study related evaluations (e.g. uncontrolled comorbidity, life expectancy < 1 year)
- Patients who have household contact with varicella-susceptible pregnant women or severely immunosuppressed individuals without history of primary varicella.

3.4.3 Study Conduct

The process to identify eligible participants, screen, consent, and randomize participants is illustrated in Figure 1 below.

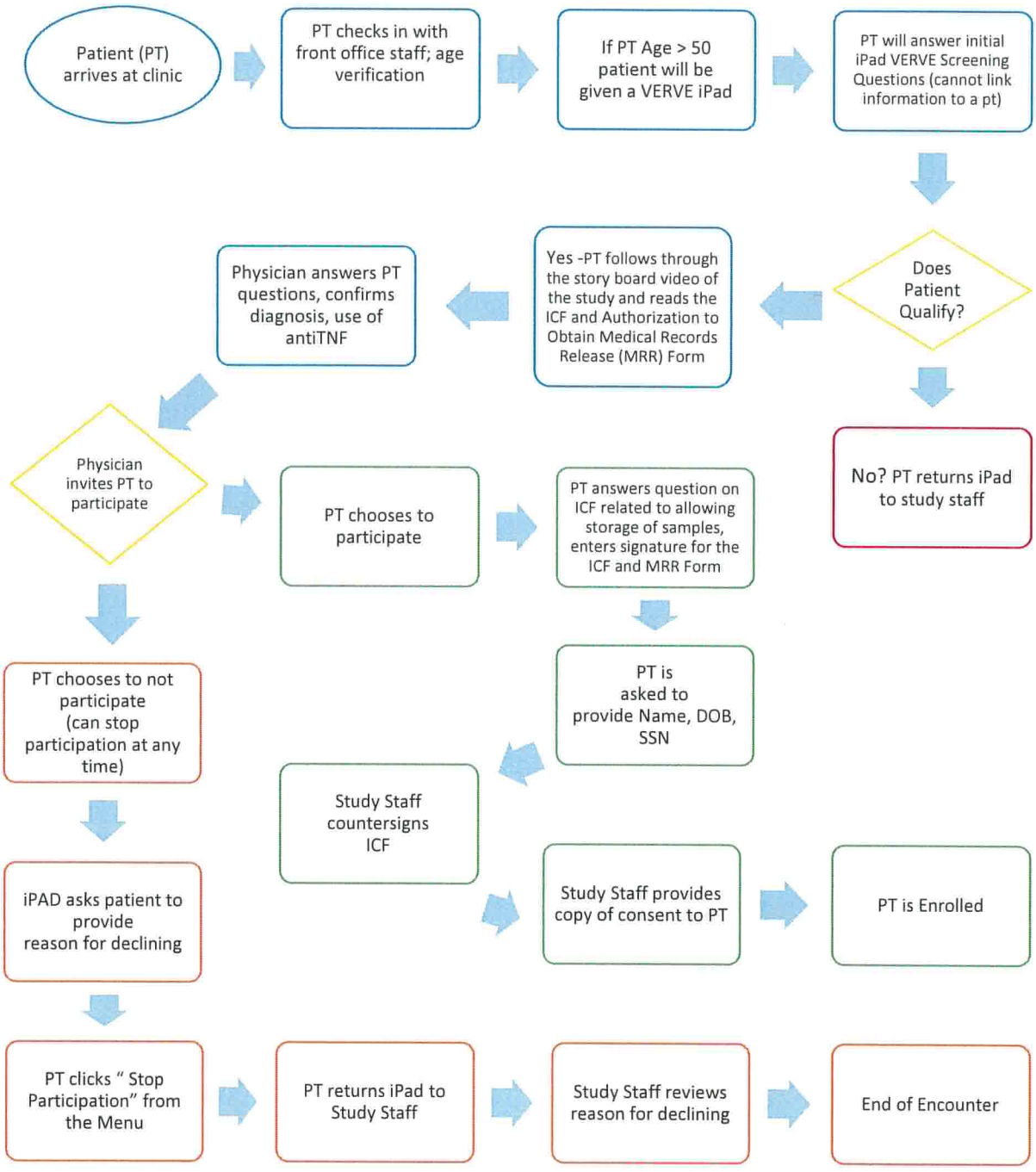


Figure 1. Flow diagram of study participant identification, consent, and randomization

3.4.4 Schedule of Study Visits

Activity per Protocol	Phase I Office-Based			Phase II Office-Based		Phase I & II Follow Up Visits			
Visits	#0 Screen*	#1 Baseline	#2 F/U	#1 Baseline	#2 F/U	F/U Phone Call Safety	Extended F/U 500 VO†	F/U via Claims Data	Unsch
Visit Time (Weeks/Years)		Wk 0	Wk 6***	Wk 0	Wk 6***	Day 3 (+2), Week 1-5, Week 6, 6 months	Year 1 & annually for 10 years**	long-term**	As Needed
Informed Consent	X			X					
Inclusion/Exclusion Criteria (Eligibility)		X		X					
Vital Signs		X	X	X	X				X
Baseline Demographics		X		X					
Screening Questionnaire		X		X					
CDAI		X	X	X	X				
RAPID3		X	X	X	X				
ELISPOT (For VZV IgG, 1 SST)	X								
Zostavax Vaccine/Placebo		X		X					
Immunogenicity (PBMC, gp-Elisa) 3 green top at screening		X	X	X	X		X		
UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma		X	X	X	X		X		
Randomization & Study Medication Administration by un-blinded staff		X		X					
Post vaccination Rash-Doctors Office as Needed									X
Safety Telephone Call						X (1000)			
Records request to confirm HZ and/or PHN			X		X	X			X
Annual clinical assessment & blood draw for patients that were given Zoster Vaccine							X (500)		
Outcomes assessment via claims data with possible medical record confirmation								X	
Photograph/Swab for PCR lesions & scabs as needed to UAB									X
Concomitant Medication		X	X	X	X	X			X
Adverse Events		X	X	X	X	X			X

*Screen = Screening, Rand = Randomization & Vaccine, F/U = Follow Up, Unsch = Unscheduled Safety Visit; ** VO = Vaccinated Only, *Indeterminate VZV results=Negative

Note: * no explicit in-person screening visit is required; VZV lab testing is expected to be accommodated at a standard of care visit
** Conditional on future funding
*** Visit window for 6 week visit includes: -2 days or +14 days (i.e. visit may occur 40 days after randomization or 6-8 weeks after randomization)
† Visit will be made at a venue other than study sites (e.g. phone-based contact with bio-specimen collection)

3.4.5 Screening

At the randomization visit, patients will be screened using screening questions. Simple screening questions will focus on whether the potential participant is a current user of one of the five approved anti-TNF therapies. Screening questions are shown in paper CRF mockups in the Appendix. For qualifying patients, the diagnosis of RA/PSA, use of anti-TNF therapy and oral glucocorticoids, and other information regarding the inclusion/exclusion criteria will be confirmed by the physician. The physician will also be available to answer any question relating to the study procedures. Basic demographic information that is de-identified will be requested for those who fail the screening or refuse consent. For factors that represent temporary exclusions (e.g. dose of background DMARDs not stable for > 30 days), rescreening at a later date is permitted without any limitations.

3.4.6 Informed Consent

Health care providers and office staff at the participating practices will receive web-based training in the informed consent process. Eligible patients will be consented by study staff before any study related activities are initiated. Patients will have the opportunity to ask the study physician any questions and can proceed to sign the consent. As part of this process, participants will be asked to provide consent to link study-related data to administrative data (e.g. Medicare) and are required to sign a VERVE study specific authorization form to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information related to study outcomes in the event these are needed.

3.4.7 Randomization to Treatment Arms

Patients will be randomized based on a 1:1 ratio to receive either the live zoster vaccine (*Zostavax®*, Merck) or placebo. Randomization/assignment will occur centrally via at the VERVE Coordinating Center in real-time. We will perform stratified randomization for 2 factors: 1) within sites and 2) use (or not) of oral glucocorticoids.

3.4.8 Blinding

This is a double-blinded study, and neither the patients nor the investigator will have knowledge of the assignment of intervention. However, Zostavax® cannot be blinded without a substantial commitment by the manufacturer (Merck), who is not willing to provide this commitment. Therefore, each site will have un-blinded site medication administration personnel delegated by the Investigator who is able to give the vaccine or placebo (saline) injection in a blinded fashion, with patients wearing an eye mask. The un-blinded medication administration personnel will have no other involvement in the study. Blinding will be maintained at least for 42 days after

vaccination at which time the primary outcome (safety) is assessed. Blinding is expected to continue through the 6 month phone visit. All patients are expected to be un-blinded after the 6 month visit but before 12 months. For patients who were vaccinated (but not those who received vaccine), will subsequently undergo un-blinded annual follow-up for clinical assessment (e.g. occurrence of herpes zoster-related events) and immunologic assessment.

Withdrawal Criteria

Subjects can withdraw from the study at any time, without prejudice to their continued care. Subjects should be withdrawn from the study if any of the following events occurs:

1. Subject withdraws his/her consent
2. The Sponsor or a regulatory agency requests withdrawal of the subject.
3. Subjects are considered lost to follow up if they do not return at 6 weeks (Phase I or Phase II patients).

If subject withdraws his/her consent or the sponsor or a regulatory agency requests withdrawal of the subject study personnel will proceed as follows; in either case study personnel will document a narrative description of the reason(s) for withdrawing or removing the subject from the study in source documents. The case report form (CRF), Study Termination, will document the primary reason for withdrawal of consent or sponsor or a regulatory agency requests to withdraw of the subject.

If subjects do not return for the 6 weeks visit in Phase I or complete 6 weeks telephone call in Phase II, the subject will be considered lost to follow up. Study personnel should continue to make at least three additional phone calls and one written correspondence to the subject in an effort to complete the 6 weeks visit. Study personnel shall document his/her effort along with a summary of the phone calls and copy of the written correspondence to be maintained in source documents.

4 Adverse Events and Potential Risks

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory

finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related (Related, Likely, Possibly or Probably Related): There is a reasonable causal relationship between study drug administration and the AE.

Not related (Not Related, Unrelated, Unlikely): There is not a reasonable causal relationship between study drug administration and the AE.

Unknown: The relationship between study drug administration and the AE cannot be determined.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)
The following table describes the complete criteria for assessing the severity of adverse events with respect to Vaccines.

A. Table for Clinical Abnormalities:

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 - 5 cm	5.1 - 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 - 5 cm and does not	5.1 - 10 cm or interferes with activity	> 10 cm or prevents daily	Necrosis

	interfere with activity		activity	

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Vital Signs *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) *	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	>40 > 104

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 - 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 - 3 loose stools or < 400 gms/24 hours	4 - 5 stools or 400 - 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Potential Risks with the Zoster Vaccine

The following problems may be caused by the study injection. If they occur, they are expected within the first 4-6 weeks from the time of injection.

- Injection under the skin of the upper arm may cause some local discomfort including such symptoms as swelling, redness, warmth, tenderness or slight bruising. This is the most common side effect of the vaccine.
- Other possible risks include the following:
    - Eye pain or visual changes
    - A rash at the site of the injection or elsewhere that can look like 'chickenpox'
    - Coughing
    - Stiff neck
    - Fever
    - A 'welt' or 'hives' at the site of injection
    - Flare of your arthritis
    - Nausea
    - Headache
    - Allergic reactions, which may be serious and may include difficulty in breathing or swallowing. If an allergic reaction occurs, subjects are to notify doctor right away, call 911, and go to the nearest ER
    - Swollen glands near the injection site that may last a few days to few weeks
    - Pain such as burning, aching, tingling, or sensitivity of one area of the body

4.1 Serious Adverse Events

A Serious Adverse Event (SAE) includes any untoward (unexpected) medical occurrence that satisfies any of the following criteria:

- It results in death (i.e., causes or leads to death)
- It is life threatening (i.e., the SAE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization
- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions)

- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above)

NOTE:

The following hospitalizations are not considered SAEs in the VERVE study:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

4.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study and randomization, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. Serious Adverse Events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Serious Adverse Events (SAEs) are collected from Randomization through Day 183 post randomization for all participants in both treatment arms. Because of a lack of biologic plausibility and because there is no longer a control group under active follow-up past day 183, there will be no SAEs collected past day 183. Outpatient (i.e. non-hospitalized) zoster related events are not considered as SAEs past day 183.

An SAE report should be completed for any event where doubt exists regarding its seriousness.

SAEs, whether related or not related to study drug, must be reported to the VERVE Coordinating Center within 24 hours of the site being notified of the event. SAEs must be

recorded on the SAE Report Form. When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be submitted also, when paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the VERVE Coordinating Center using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

4.1.2 Suspected Unexpected Serious Adverse Reactions (SUSARS)

The Verve Coordinating Center will report all received SUSARS, and increased rates of expected Serious Adverse Reactions, within 15 days of knowledge of these events (within 7 days for any SUSAR that is life-threatening or results in death) to CBER and all participating investigators.

4.2 Non Serious Adverse Events

A *non-serious adverse event* is an AE not classified as serious.

4.2.1 Non Serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug and will extend through the 6 week follow-up visit. No AE reporting beyond the 6 week visit is required. Non Serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. However only new or worsening AEs reported after initiation of study drug will be reported.

Non-Serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 4.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

4.3 Study Endpoints

4.3.1 Primary Endpoint

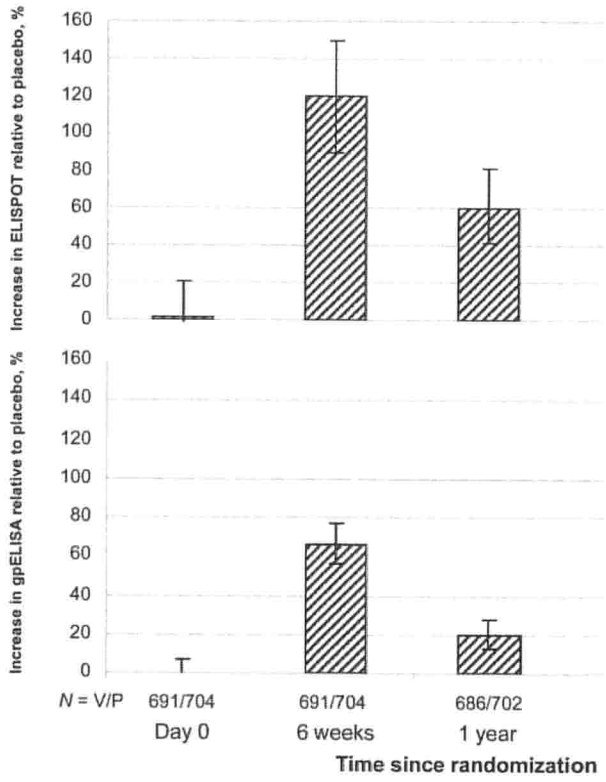
Definition- Evaluation of vaccine immunogenicity

Although vaccination for VZV results in the development of robust T and B cell immunity, studies suggest that T cell immunity is best correlated with protection against both primary VZV infection and later reactivation. For example, with regard to primary infection, children with agammaglobulinemia generally have uncomplicated varicella, whereas children with T cell deficiencies are more likely to suffer from progressive disseminated varicella.[22] With regard to reactivation, and unlike VZV-antibody titers which do not decline with age, VZV-specific T cells frequencies decline significantly with age, suggesting that the reduction in T cell immunity is the underlying factor for VZV reactivation.[23-25] More recent studies further support the strong correlation between VZV-specific T cell frequencies and protection from clinical HZ events, including the immunologic substudy of the SPS in which higher frequencies of VZV-specific T cells at 6 weeks after vaccination were associated with decreased subsequent HZ risk.[26] No such association was observed with gpELISA titers. Further, among patients who develop HZ, higher VZV-specific T cells frequencies have been shown to be associated with lessened HZ severity and a decreased risk of PHN. Conversely, higher VZV gp-ELISA titers correlate with

more severe HZ disease, likely as they result from the enhanced viral replication during active infection. Given that these data demonstrate that VZV-specific T cell frequency measures are predictive of HZ immunity, we will use this approach as our primary immunologic measure in the proposed VERVE trial.[27]

There is more than one method to measure VZV-specific T-cell responses. Responder Cell Frequency (RCF) has been used in some past VZV trials and historically was considered the most accepted measurement of T cell responses.[28] While this assay has played an instrumental in advancing our understanding of cell-mediated immunity (CMI) to VZV, it is cumbersome to perform and requires a time consuming approach that is biased towards measuring CD4 T cell responses. More recently, the enzyme-linked immunosorbent spot (ELISPOT) assay for the enumeration of cytokine-producing T cells has become one of the most commonly used immunoassays for assessing CMI in clinical trials of vaccine efficacy. In this assay, the number of observed spots is a direct measure of the number of responding cells, and the size of the spot is a measure of the amount of product (e.g. interferon-gamma) secreted by the cell. This technique has several key advantages: 1) it is highly quantitative (one spot=1 responding cell); 2) it is qualitative (size of spot is an indicator of the amount of the secreted product); 3) has a lower limit of detection than other available methods; 4) can be easily standardized across time and laboratories; 5) can detect multiple products simultaneously; 6) provides results within 24 hrs: and 7) is relatively inexpensive[29].

The results from the immunologic substudy of the SPS demonstrated the strong relationship between vaccination and change in ELISPOT.[26] A rigorous study by Smith and colleagues[30] has validated the use of IFNg ELISPOT for the assessment of VZV-specific CMI. The study demonstrated that ELISPOT can be used to evaluate responses using PBMCs that are freshly isolated, thawed after being cryopreserved, or isolated from blood that was stored at 4^0C overnight. All these sources of PBMCs gave equivalent results. Additional recent studies have also showed a tight correlation between RCF and ELISPOT.[27, 31] Therefore, we will measure



As a complementary lab-based outcome to ELISPOT, VZV gp-specific antibody titers are a surrogate, lab-based measure of vaccine immunogenicity and also have been used in prior Zostavax® clinical trials, although they have a weaker correlation with HZ incidence and protection.[27] Importantly, though, the FDA has accepted this antibody response as a marker of protection. Although the validity of gpELISA titers as a clinically relevant correlate of protection against HZ remains under intense debate,[32] we will measure VZV gp-specific IgG titers as a secondary outcome of this trial using established ELISA protocols from prior phase III Zostavax studies.

4.3.2 Procedures for Reporting and Recording

Ascertainment of VZV events within 42 Days

VZV events: Potential VZV-like events during the study time-period include (a) vaccine-strain infection presenting locally at the injection site (likely to be non-serious) or disseminated in the form of a multi-dermatomal rash with systemic symptoms such as fever, encephalitis or other CNS disease (captured as SAEs); or (b) Herpes zoster (i.e. reactivation of varicella unrelated to vaccination) that could also present during this time-period either as local or disseminated disease. All potential VZV-like events occurring within the first 42 days should be followed clinically with repeated observations until resolution or stability. We will distinguish non-vaccine related HZ from cases of local or disseminated VZV due to the vaccine strain using methods as described below.

Case Definitions for Suspected and Confirmed Cases of Vaccine-strain VZV events [part of composite primary outcome]

Definition of suspected vaccine-strain VZV case: patients who within 42 days of vaccination, have either (a) Vesicular rash in dermatomal distribution OR (b) non-vesicular rash with pain in dermatomal distribution OR (c) other VZV diagnosis by treating specialist (e.g. ocular VZV diagnosed by ophthalmologist). VZV rashes will typically begin with maculopapular lesions and progress to vesicles. For all suspected cases, confirmation of vaccine strain virus will be sought as below.

Definition of confirmed vaccine-strain VZV case: any suspected case confirmed by PCR for vaccine-strain (Oka) virus.

Procedure for evaluation of a suspected vaccine-strain VZV case:

All suspected vaccine-strain VZV cases will be evaluated while maintaining the study blind. For any rash with or without pain that develops within the 6 weeks following vaccination, participants will be instructed to immediately contact the site physician for evaluation and also contact the UAB Coordinating Center. Sites also will be instructed to take photos of the rash and will collect biologic specimens (lesion swab, collected according to the Manual of Operating Procedures). These specimens will be transferred to viral transport media (provided by the study) and then sent for VZV PCR analysis performed at UAB (Whitley lab, co-investigator on the trial and part of the VERVE steering committee). If PCR confirms VZV infection, differentiation of wild type VZV from vaccine-strain (Oka) virus will be performed at the Center for Disease Control (Schmid's lab at the CDC).[5, 27] The simple procedure to collect samples from a VZV-suspected rash are similar to that used within the SPS studies and are described in the VERVE MOP. A test kit will be provided by the study to sites for this purpose.

For the minority of specimens sent for laboratory diagnosis for which material is inadequate for virus isolation and/or PCR analysis (as determined by the absence of detectable cellular DNA [i.e., the 13-globin gene] following PCR amplification), a Case Adjudication committee that is blinded to all microbiologic test results will review all clinical data from the VERVE CRFs and photographs in order to confirm investigator rash classification as meeting the suspect case definition. For ocular cases, clinical diagnosis by ophthalmologists (obtained from medical records) will be accepted.

For the very small number of cases needing clinical adjudication (non-cutaneous cases and cutaneous-cases lacking adequate laboratory specimens), it will be unknown if they are due to vaccine-strain virus. Thus, they will be able to meet the case definition for suspected vaccine-strain VZV, but not PCR-confirmed vaccine-strain VZV. Therefore, these cases will be included in the outcome events analyzed for the primary outcome, assuming they are adjudicated as probable or confirmed following clinical adjudication based upon clinical data, including digital images (if available). A clinician with expertise in identifying varicella infection will be appointed as a safety monitor and will be responsible for initial triage and clinical adjudication, with additional input from the DSMB as indicated. Clinically adjudicated cases will be excluded as part of a sensitivity analysis that will be reported as a secondary endpoint of the trial of PCR-confirmed vaccine-strain VZV events.

4.3.3 Ascertainment of Serious Adverse Events within 42 Days

If an SAE occurs, the site investigators will report this to the Coordinating Center within 24 hours of receipt of the information by the site. The site will complete a VERVE SAE Report form, even

if the data are incomplete, until the event is considered resolved or stable. The DSMB will periodically review these data (see below).

4.3.4 SAE Follow-up

All SAEs that are encountered during the protocol-specified AE reporting period (i.e. through 6 months) should be actively followed to their resolutions, or until the investigator assesses them as stable, or the subject is lost to follow-up. Resolution of SAEs (with dates) should be documented on the appropriate AE or SAE CRF page and in the subject's medical record to facilitate source data verification.

SAEs may be followed up by telephone, fax, electronic mail, and/or additional visit(s) to obtain additional case details deemed necessary to appropriately evaluate the SAE report. Medical records for events occurring between the baseline and 6 week follow-up visits will be obtained by study sites. If medical records cannot be obtained by study sites for events occurring within these 6 weeks, and for all events occurring after the 6 week visit, the VERVE-assigned Call Center will have primary responsibility for obtaining medical records. This will include hospital records if the patient has been hospitalized and any additional medical record data needed that has not been directly collected by the site personnel.

SAEs can be reported spontaneously at any point during the first 42 days after receipt of the vaccine injection.

5 Secondary Endpoints

5.1 Definition

The secondary endpoints of the study include the following:

- Longer-term Clinical Effectiveness - Ascertainment of Herpes Zoster Beyond 42 Days

  After the first 42 days following vaccination (a risk window defined by the incubation period for VZV infection and subsequently used by all major zoster vaccine trials), we will continue to follow all trial participants who are enrolled in a health plan with data that can be linked to VERVE (e.g. Medicare, WellPoint). Given the age requirement of the study of 50+, we estimated that approximately 50% of the overall trial population will be linkable to administrative health plan data to assess the longer term effectiveness of the vaccine. Incident HZ cases occurring more than 42 days following vaccination will be identified from administrative claims data by the first HZ diagnosis code occurring during follow-up (ICD-9-CM code 052.* (chickenpox), 053.* (herpes zoster), and ICD 10

diagnosis code B02 beginning 2014 during hospitalization or a physician office visit that was accompanied by a pharmacy claim for anti-viral treatment (acyclovir, famciclovir, valacyclovir) within +-7 days. The positive predictive value (PPV) of the HZ diagnosis code alone to identify a new case of HZ (using medical record review as a gold standard) ranges between 85 and 100%, depending on the study and the age group (PPV higher for older individuals).[3, 33] The additional requirement for anti-viral drug use was applied to improve the PPV. An alternate case definition that requires only a HZ diagnosis code from inpatient or physician office visit claims without the requirement for anti-viral drug use will also be used. These data will be used to assess both the effectiveness of vaccination beyond 42 days, comparing vaccinated vs. non-vaccinated patients. An additional comparator group of non-participants (i.e. those not approached for the trial, because their treating rheumatologists did not participate as study sites) will also be examined in the health plan data. These analyses will assess when the immunity to HZ associated with vaccination wanes, as evidenced by a rising incidence of HZ that approaches the unvaccinated rate of HZ. The clinical implications of this secondary aim are to inform the potential need for re-vaccinating patients some years after initial vaccination. These data will also be used to assess the generalizability of the study population enrolled in the trial.

- Safety
  A composite outcome of all serious adverse events (SAEs) AND non-serious vaccine-strain VZV events within 42 days of vaccination. Serious adverse events of interest include all serious adverse events that satisfy the FDA-accepted definition of SAEs (results in death, life threatening, results in or prolongs hospitalization, etc.). Potential VZV events during the study time-period include vaccine-strain infection presenting locally at the injection site (likely to be non-serious) or disseminated in the form of a multi-dermatomal rash with systemic symptoms such as fever, encephalitis or other CNS disease (captured as SAEs). Although unlikely, herpes zoster (i.e. reactivation of varicella unrelated to vaccination) or primary infection could also present during this time-period either as local or disseminated disease. We will distinguish non-vaccine related HZ from cases of local or disseminated VZV due to the vaccine strain using methods as described below.

- Occurrence of herpes zoster from 6 weeks and beyond using linked administrative claims data (clinical measure of long-term vaccine effectiveness)

- RA disease activity related measures including CDAI and RAPID3 (measured at baseline and 6 weeks)[34-35]
- Tolerability of vaccination using patient diaries (Phase I using data collected at 6 week in-person visit)

5.2 Additional Procedures for Reporting and Recording Endpoints

5.2.1 Lab-based Outcome Measures (primary endpoint)

Endpoints of the study include mechanistic studies to evaluate vaccine immunogenicity using surrogate measures of vaccine effectiveness including VZV gp-specific antibody titers and VZV-specific T cell responses

Although VZV gp-specific antibody titers do not always correlate with HZ incidence or protection,[27, 32] this outcome has been used in prior Zostavax® clinical trials and validated as a surrogate measure of vaccine immunogenicity and an outcome recommended by FDA to be assessed in our pre-study planning consultations with them. VZV gp-specific IgG titers will be measured using established ELISA protocols from prior phase III Zostavax® studies. Importantly, prior studies documented that VZV-antigen specific cell-mediated immunity correlates both with vaccination and the risk of later zoster occurrence in that the susceptibility to HZ negatively correlates with the frequency of VZV-specific T cells. Previously, Responder Cell Frequency (RCF) was considered the most accepted measurement of such T cell responses. However, more recent studies have shown a tight correlation between RCF and ELISPOT.[27, 32] Therefore, we will measure frequency of VZV-specific T cells using ELISPOT. The advantages of this approach are: 1) requirement for fewer cells; 2) quicker turnaround; and 3) technical simplicity.

Analytic methods: Peripheral blood mononuclear cells (PBMCs) will be collected from the first 200 vaccinated patients at screening, and then again at 6 weeks post vaccination, and shipped to Vaccine and Gene Therapy Institute (VGTI) (Messaoudi lab). [Samples will be collected for these lab-based outcomes for the first 250 patients, but the PBMC samples will only be analyzed after the participants have completed the study at 6 weeks at which time their randomization status will be known.]

PBMCs will be stimulated with VZV antigen and the frequency of IFNγ-secreting T cells will be determined using ELISPOT as previously described.[26] Samples for gp-ELISA measurements will be collected at the same time points and also evaluated at VGTI. Post-vaccination

ELISPOT results will be compared to baseline pre-vaccination level for all vaccinated patients using Poisson models along with the generalized estimating equations (GEE) for estimating the model parameters for correlated data. If excessive zero counts are found on the ELISPOT data, we will consider a zero-inflated Poisson (ZIP) model or negative binomial model if over-dispersion persists. Post-vaccination ELISA results will be compared using paired t-test. The normality assumption for paired t-test will be assessed by the Kolmogorov-Simirnov test. Transformation or non-parametric methods, e.g. Wilcoxon singed rank sum test, will be considered if the normal assumption does not hold.

For VZV-specific ELISPOT responses, based on the prior Zostavax® immunogenicity study[26] we anticipate detecting 30 VZV-specific T cells/10^6 PBMCs prior to vaccination. This number should increase by an average of 40 VZV-specific T cells/10^6 PBMCs at 6 weeks. There is also some subject-to-subject variation in VZV-specific T cells/10^6 PBMCs (standard deviation of 90/10^6 PBMCs) at baseline, and it is unclear how these data reflect findings in RA patients using immunosuppressives. Assuming baseline and vaccine related responses are similar, or even 50% reduced compared to the Levin et al data, we would anticipate needing 217-333 patients to achieve 80% power to observe an approximate doubling of VZV specific cells above baseline. The data obtained will be used to formulate hypotheses and correlate these VZV ELISPOT measures with long-term vaccine efficacy that will be pursued using samples from the biorepository (baseline) and additional bio-specimens to be collected at yearly intervals after initial immunization. These samples will allow for examination of waning immunologic protection over time.

5.3 Long-term Clinical Effectiveness---Ascertainment of Herpes Zoster Beyond 42 Days (secondary endpoint)

Incident HZ cases beyond 6 weeks following vaccination will be identified from claims data by the first HZ diagnosis code occurring during follow-up (ICD-9-CM code 053 and 0.52 and ICD 10 diagnosis codes beginning 2014) in an inpatient or physician office visit claim that was accompanied by a pharmacy claim for anti-viral treatment (acyclovir, famciclovir, valacyclovir) within 7 days before or after. The positive predictive value (PPV) of the HZ diagnosis code alone to identify a new case of HZ (using medical record review as a gold standard) has been shown to range between 85 and 100%, depending on the study and the age group (PPV higher for older individuals).[3, 33] The additional requirement for anti-viral drug use was applied to improve the PPV. An alternate case definition that requires only a HZ diagnosis code from inpatient or physician office visit claims without the requirement for anti-viral drug use will also be used within sensitivity analyses. These data will be used to assess both the effectiveness of

vaccination beyond 42 days comparing the vaccinated vs. non-vaccinated patients. It will also be used to assess when the immunity to HZ associated with vaccination wanes, as evidenced by a rising incidence of HZ that approaches the unvaccinated rate of HZ.

6 Statistical Analysis Plan

6.1 Sample Size and Analysis

Drop out from the study and associated missing data is expected to be minimal given that the primary outcome of interest will be assessed 42 days later. Moreover, participants will be screened at baseline to exclude those with uncontrolled comorbidities, planning surgery or other procedures requiring hospitalization, with an active infection, or planned absence resulting in an inability to return or participate in follow up.

6.2 Primary Outcome (SA1): Immunogenicity

The primary outcome for the trial will be the change in ELISPOT response from baseline to week 6. The primary comparison will be the difference in the change score between the placebo and vaccine groups, assessed using a two-group t-test. Based upon results seen in the Levin et al study, 1000 total participants (500 per group) will achieve at least 80% power to detect a difference of 29.7 between the active and placebo groups, with an alpha = 0.05 and SD of 180. This difference represents a 30% reduction in the response seen in Levin, to allow for a reduced response in participants with RA. Should the ELISPOT response be closer to the response observed in Levin (38.5), the 1000 participants allows for an increase in the observed SD of the difference up to 200. In the unexpected event that the ELIPOST response in these participants be as low as 60% of what was seen in Levin (a difference of 25.3), there is still 70% power to detect this difference.

Samples for gp-ELISA measurements will be collected at the same 0 and 6 week time points and also annually and evaluated at UCR based on the data from the SPS study[36]. Based upon the sample size required to adequately power the ELISPOT primary outcome, this sample size will yield more than 80% power to detect an increase of 175.0 in IgG titers 6 weeks post vaccination compared to the placebo group (assuming from Levin et. al. 2008, a standard deviation of 950; α=0.05 using a two-sided t-test). Should there be a lower response in the RA vaccinated group of 150.0, there is still 80% power to detect with an SD of 850, α = 0.05.

6.3 Secondary Outcomes (SA2, SA3): Clinical effectiveness and safety

The study is adequately powered to study the primary aim (SA1) for both the primary ELISPOT outcome and the secondary gp-ELISA outcome. Power calculations using data from the 1000 participants (500 per group) for SA2 and SA3 are described below.

For SA2 (longer term effectiveness of vaccination), and examining the risk of HZ and PHN after 6 weeks following vaccination, cumulative event rates for each outcome will be calculated as the product-limit estimator and a log-rank test will be used to assess whether the cumulative event rates for the vaccine and place groups differ. With 500 participants per group, and a placebo cumulative incidence of 5% (over the entire study follow-up period), there is 80% power using a two-sided test to detect a difference in the active arm lower than 1.8%. This relative risk reduction of [100 - (1.8 / 5) = 64%] is compatible with the benefit seen in the zoster vaccine trials in healthy older adults. Because HZ risk is associated with the use of immunosuppressive agents, changes in patients' treatment regimen, e.g., discontinuing anti-TNF therapies, switching to other agent(s) may increase or decrease their HZ risk. To control for such changes in risk factors for HZ, both an ITT analysis as well as a separate time-varying covariate Cox-proportional hazards regression model will be used to examine the impact of zoster vaccine on the secondary efficacy outcome. Power is substantially better when using the alternate comparator group of patients not approached for the trial but available to us within the health plan data. Additionally, our expectation is that we will be able to continue to follow participants beyond the end of the study period through this link with administrative health plan data (conditional on modest future funding to purchase the data).

For SA3 (non-inferiority of safety comparing vaccinated to unvaccinated patients at 6 weeks), if the observed event rate in the placebo group is 2.0%, the event rate in the vaccine group could go as high as 2.46% for the upper bound of the 95% confidence interval of the difference between the vaccine and placebo groups to be less than the acceptable non-inferiority (NI) margin of 2.0%. If the placebo event rate is lower at 1.5%, the active group may go as high a 2.1% to maintain a NI margin less than 2.0% for the confidence interval on the difference. In the unlikely event the placebo event rate is as high as 3.0%, the vaccine group could be as high as 3.6% for the upper bound on the confidence interval to be less than a still acceptable 2.5%. Thus, we are well powered in SA3 to detect a reasonable non-inferiority margin for the composite safety outcome of SAEs and vaccine strain-associated clinical HZ events.

The secondary outcomes of the trial are a composite safety outcome, rather than an efficacy outcome for which an intent-to-treat population would be most relevant. Therefore, the safety

population used for analysis will contain all randomized participants that received the study injection. Any participant with documented evidence of receipt of the wrong study medication will be analyzed as-treated. The number and proportion (%) of subjects experiencing the primary outcome will be calculated with risk differences and associated 95% confidence intervals and compared using a test of proportions for non-inferiority according to vaccination group (vaccine vs. placebo).

6.4 Statistical Methods

Descriptive analyses (means, medians, standard deviations, frequency distributions) and correlation analyses (Pearson or Spearman rank correlations) will be conducted to assess and describe the cohort. Baseline comparability will be assessed [parametric and nonparametric one factor (treatment group) analysis of variance] and examination of the correlates of disease history (Pearson or Spearman rank correlations) will be investigated.

6.4.1 Primary Outcome

Geometric means, 95% CI and percentage increase in geometric mean in vaccine and placebo recipients will be calculated at each time point. The primary outcome will be a two-group t-test between the active and placebo group, comparing the difference in the ELISPOT response from baseline to week 6. In addition, age adjusted and other covariate adjusted models will be assessed using an analysis of covariance model (ANCOVA) that included the log transformed VZV-specific response as the response variable and treatment or subgroup as independent variables. In addition to age, other covariates considered will be sex, time point(s) after vaccination, immune response at baseline, and specific anti-TNF medication.

6.4.2 Secondary Outcomes

For the secondary outcomes, we will compare the proportion of participants experiencing SAEs and vaccine-strain VZV-like infections occurring during the first 42 days and at later time points after vaccination. The 95% confidence interval for incidence rates in each group (vaccinated versus unvaccinated) will be calculated using the exact binomial method. The 95% confidence interval associated with the rate difference will be calculated using an asymptotic method for the difference of two binomial proportions. An estimate of the odds for SAE or VZV-like infections calculated as unadjusted OR with 95% CI as well as adjusted odds ratios considering covariates listed in C.8.2.1 above using logistic regression. Time to SAE and VZV-like infections will be assessed using Cox-proportional hazards models, adjusted for covariates listed in above.

6.5 Stopping Rules and Interim Analyses

6.5.1 Stopping Rules for Confirmed Vaccine-Strain VZV Cases

The study will be evaluated after the first 100 and 250 participants have been enrolled. Given that the expected rates of confirmed vaccine-strain VZV cases would be low (1 in 1000 participants), the trial will be stopped if 3 vaccine-strain confirmed VZV cases occur in the first 100 vaccinated participants (with at least 2 being in the active vaccine group) or 5 in the first 250 participants (with at least 3 being in the active vaccine group).

Rationale for clinically meaningful, count based stopping rules: The expectation is that the number of confirmed vaccine-strain VZV cases in the first 100 and 250 participants will not be adequate for formal statistical testing.

Enrollment between phases of the trial will be continuous, meaning that after each of the phase 1a and phase 1b recruitment targets have been met, the DSMB and FDA will be provided the data to consider advancing the study to the next phase. During this period of time (expected to be relatively short [e.g. 1-2 months]), enrollment may continue under the prior inclusion criteria and need not be halted.

6.5.2 Interim analyses

It is not expected that this trial will stop early or that the DSMB will want to excessively spend Type I error for interim monitoring following the close of Phase I (though should the DMSB request an interim analysis prior to start of the trial, appropriate adjustments can be made). However, at this stage no formal statistical tests based upon the safety data will be conducted following phase I. Achieving a statistically significant difference for an interim analysis on 250 participants (125 per group) that would be adjusted for multiple testing (i.e. $p<0.0001$ or 99.99% upper bound on a CI less than an acceptable margin) is highly unlikely. With an expected event rate of 2.0% in the placebo group, we would expect to see less than 3 combined SAEs in each group (5 total). To detect any statistically significant difference between the groups with an unadjusted Fisher's Exact test, all SAEs would have to have occurred in the active vaccination group to achieve a statistically significant p-value < 0.02, and with an adjustment for multiple testing for an interim analysis, we would require the p-value to be < 0.0001, which is not possible to observe with a sample size of 125 per group at the end of phase 1. Considering a confidence interval on the difference in proportions, with equal 2% event rates in the active and placebo groups the upper bound would approach 7% for an equivalent of a 99.99% CI. It is not

possible to achieve a non-inferiority margin similar to the 1.25% proposed due to the small sample size at the conclusion of phase 1 (the minimum upper bound possible would be associated with 1 event in the active group and 0 events in the placebo group for an upper bound of 0.0395 or 3.95%).

6.5.3 Interim Analysis for Sample Size Evaluation

Due to the FDA approval of Shingrix and the expected impact on enrollment into the VERVE trial, it may be necessary to perform an interim analysis to determine if the data that has been collected in VERVE aligns with the estimated values utilized for power and sample size estimation during study planning. VERVE will monitor recruitment from August – October 2018 and compare it to the same time frame in 2017 immediately prior to Shingrix approval. The results will be presented to and discussed with the DSMB at its December 2018 meeting (or at the next meeting thereafter). If VERVE recruitment has slowed appreciably, the DSMB will likely request an interim analysis.

The interim analysis will be limited to estimation of the geometric mean fold change (GMFC) and standard deviation of the GMFC from baseline to week 6 in the active and placebo VERVE groups for the IgG (ELISPOT) and IFN (gp-ELISA) primary outcomes as described in section 6.4.1. As this was not a planned interim analysis, the alpha spending approach of Lan-DeMets (Stat Biosci (2009) 1: 95–111) will be used for 1 interim analysis at 50% of the data collection (N=500 / 1000) reaching the primary endpoint of 6 weeks. The interim alpha level will be set to 0.002787, with the final alpha testing family-wise error rate being maintained at alpha = 0.05. If statistical significance is not met at the interim analysis, the observed values at the interim analysis will be used to determine if the study sample size goal of 1000 can be adjusted downward to include fewer participants and still achieve statistical significance at for the primary outcomes.

6.6 Description of Objectives and Endpoints

Given the 1) widespread use of anti-TNF therapy, 2) the increased risk of HZ in RA patients, 3) evidence that current Zostavax® uptake is poor among RA patients; and 4) preliminary data suggesting that the use of zoster vaccine may be safe and effective in these patients, we believe it is of great public health importance to prospectively evaluate the immunogenicity, safety and effectiveness of Zostavax® in RA patients using anti-TNF therapy.

6.6.1 Analysis Population for Primary Outcome

With a follow up period of 1 year and limited data collection form set, it is anticipated that the amount of missing data will be low. Using the safety population, all participants will be included

in the analysis in the arm in which they were randomized to at the time of the injection. If the endpoint (event Yes/No) is missing for any reason (e.g. lost to follow-up) multiple analyses will be conducted: as observed, using only those with confirmed endpoint data and sensitivity analyses to determine the effect of assuming an event occurred and that an event did not occur. Based on the understanding that this is not always possible, the following populations will be formed for the purpose of data analysis:

6.7 Statistical Methods

For the primary outcome, we will compare the percentages of SAEs and vaccine-strain VZV-like infections occurring during the first 42 days after vaccination. The 95% confidence interval for incidence rates in each group (vaccinated versus unvaccinated) will be calculated using the exact binomial method. The 95% confidence interval associated with the rate difference will be calculated using an asymptotic method for the difference of two binomial proportions. The primary hypothesis to be tested is that the cumulative incidence of the primary study outcome occurring in the vaccinated arm will be non-inferior (i.e. no higher) than the 1.25% pre-specified non-inferiority margin compared to the control group. This non-inferiority margin was established based upon clinical input from the expert panel of virologists, immunologists, and rheumatologists that created the VERVE study protocol. The number and proportion (%) of subjects experiencing the primary outcome will be calculated with risk differences and associated 95% confidence intervals and compared using a test of proportions for non-inferiority according to vaccination group (vaccine vs. placebo). Descriptive analyses (means, medians, standard deviations, frequency distributions) and correlation analyses (Pearson or Spearman rank correlations) will be conducted to assess and describe the cohort. Baseline comparability will be assessed [parametric and nonparametric one factor (treatment group) analysis of variance] and examination of the correlates of disease history (Pearson or Spearman rank correlations) will be investigated.

6.7.1 Analysis Population for Primary Outcome

6.7.1.1 Safety Population: *The safety population included in the primary analysis consists of everyone who receives injection either with the vaccine or placebo. Given that the injection will generally be given on the same day as randomization, the as-randomized and the safety populations are expected to be nearly identical.*

6.7.1.2 Pre-specified Sub-group Analysis for the Primary Outcome

Stratified analyses will be conducted by age (in 10 year age groups, 50-59, 60-60, etc), by glucocorticoid use and dose at the time of study injection, and by specific anti-TNF drug used at the time of vaccination

6.7.2 Handling of Missing Data for Primary Outcome

Again, with a short follow up period of 42 days and limited data collection form set, it is anticipated that the amount of missing data will be low. Using the safety population, all participants will be included in the analysis in the arm in which they were randomized to at the time of the injection. If the endpoint (event Yes/No) is missing for any reason (e.g. lost to follow-up) multiple analyses will be conducted: as observed, using only those with confirmed endpoint data and sensitivity analyses to determine the effect of assuming an event occurred and that an event did not occur.

7 Ethics Considerations

7.1 Informed Consent

Subject's Informed Consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki. Prior to obtaining Informed Consent, information will be given a level of complexity understandable to the subject in both oral and written form by the investigator or designee. Each subject will have the opportunity to discuss the study and its alternatives with the site investigator or sub-investigator(s).

Prior to participation in the study, the written Informed Consent Form will be signed by the subject, or his/her legal representative (if the latter is approved by the IRB), and by the person who conducted the Informed Consent discussion (Investigator or sub investigator). The subject or his/her legal representative will receive a paper copy of the Informed Consent Form. As part of the consent process, each subject will consent to direct access to his/her medical records for study-related monitoring, auditing, IRB review, and regulatory inspection. If the Informed

Consent form is amended during the study, the Investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the governing IRB.

The subject may withdraw their consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. No identifiable patient data will be collected without having obtained consent for participation in the study.

8 DSMB Governance

An independent Data and Safety Monitoring Committee (DSMB), comprised of members without conflicts of interest with the VERVE study, will be formed for this trial. The 5-member DSMB is exposed to have a composition that includes infectious disease physicians with expertise in virology, an epidemiologist, a statistician, and a rheumatologist. The DSMB will be responsible for evaluating scientific issues related to the study. The DSMB will remain un-blinded to treatment allocation when monitoring adverse events.

The DSMB will receive data periodically (e.g. quarterly) including pre-specified time points including after the first 100 patients, the first 250 patients, and quarterly for the remaining 750 patients. Enrollment will not need to be halted during periods of DSMB consideration, but explicit DSMB and FDA approval is required to advance the inclusion criteria to the next phase of the study (Ia to Ib, and Ib to II).

The pre-specified stopping rules outlined in section 6.5 will be adhered to. The VERVE steering committee believes that risk-benefit assessment would be best evaluated by the DSMB over the course of the trial and guided by the pre-specified stopping rules regarding case definitions for VZV events in this protocol. The DSMB may recommend at any point that the study be stopped if the risk-benefit assessment for continuance is deemed unfavorable.

9 Institutional Review Boards

The study will be conducted only in the U.S. and under the auspices of a local (e.g. university) or central IRB, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The Investigator will ensure that an appropriately constituted IRB that complies with the requirements of the current ICH-GCP version or applicable regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to

initiation of the study, the Investigator will forward copies of the protocol, Informed Consent form, Investigator's Brochure, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB for its review and approval. Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB for the protocol. The Investigator will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB as allowed. As part of the IRB requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB (based on the Committee's requirements), at intervals appropriate to the degree of subject risk involved but no less than once per year. The Investigator should provide a final report to the IRB following study completion. To the maximal extend possible, these functions will be assisted by the central VERVE study personnel at the Coordinating Center.

10 Protocol Amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective. Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by the IRB and the regulatory authorities (if required), prior to being implemented.

11 Regulatory and Administrative Considerations

11.1 Adherence to protocol

In order to assure the successful conduct and completion of this study, all sites must adhere to certain performance standards. The UAB Coordinating Center and the VERVE Steering Committee will jointly set performance standards and monitor site activities to assure that these standards are met. When a performance problem exists, several steps will be taken to resolve the problem. First, the program coordinator will communicate the problem to the site. At this stage, the coordinating center will work with site personnel to identify causes of the problem and offer solutions. If the problem continues, additional training will be considered. In cases of

problems of sufficient severity or intractable problems that are not resolved by the procedures described above, an investigational site visit may be necessary and will be determined on a case by case basis. Each of the clinical sites will require local IRB approval and documentation of this will be forwarded to the Coordinating Center prior to start-up and on an annual basis for continuing review. The UAB IRB or governing local or central IRB will address any issues with each of the individual sites if needed.

11.2 Trial Monitoring

The groups charged with monitoring the various aspects of the study will be: the VERVE Steering Committee, the Data Safety Monitoring Board (expected to be appointed by the NIH, conditional on NIH funding), UAB IRB (for the Coordinating Center) and the UAB Coordinating Center. The Steering Committee will monitor the operational aspects of the study at periodic intervals as well as performance of participating clinical sites and the quality of the data collected as needed. The Steering Committee will also oversee the publication and presentation of all data from the study. Permission must be granted by the Steering Committee before data from the study can be used for presentation or publication. Continuous remote monitoring of study data quality will be jointly performed by the Coordinating Center and associated business associated as completed electronic case report forms are transmitted from the participating clinical sites. The UAB Coordinating Center will monitor the frequency of data problems such as missing data, unusual values and inconsistent data or data not received.

11.3 Data Handling

Each site will be provided with access to the data entry application (Velos ®) in order to optimize the management of the large number of subjects and to allow timely submission of data to a central database at the Coordinating Center. A security system will be maintained that prevents unauthorized access to data and each site staff will have a unique sign on code. Visit data will be captured through the Velos ® and the Coordinating Center staff will have direct access to this data to review and monitor on a frequent basis. The local study coordinator or site staff will oversee entry of all study data. The Coordinating Center will review all case report forms as they are received for accuracy, completeness, consistency between related data items and adherence to protocol ensuring data quality. Data query reports, such as unresolved data problems and missing/overdue forms, will be sent to the participating sites for processing. Data quality summaries will be generated monthly and reviewed. The reports will include comparison of data quality across sites. The Coordinating Center will communicate commonly occurring problems to all sites and work directly with specific sites where higher error rates are detected in order to improve data quality. Continued data quality problems may result in placing sites on

probation. Sites cannot be paid for a visit until all case report forms have been submitted and deemed acceptable by the Coordinating Center.

Data transmission must occur according to the schedule determined by the Coordinating Center. The schedule for submission is five working days after the visit occurs, although immediate electronic submission is anticipated for the vast majority of data. When necessary, the Coordinating Center may require supporting documentation from the medical records obtained and provided by the study sites (if an SAE is initially reported to the site) or VERVE Call Center. At times, the five working days timeframe will not allow enough time to obtain this data.

11.4 Termination of the study and Protocol Amendments

Both the Coordinating Center and the local investigator reserve the right to terminate the study, according to the study contract. The investigator should notify the *IRB* in writing of the trial's completion or early termination and send a copy of the notification to the Coordinating Center IRB. Protocol amendments must be made only with the prior approval of Executive Steering Committee and the Coordinating Center. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The local *IRB* must be informed of all amendments and give approval for any amendments likely to affect the safety of the subjects or the conduct of the trial. The investigator must send a copy of the approval letter from the local *IRB* to the Coordinating Center's IRB.

11.5 Audit and Inspection

On-site inspections are not planned for this trial. However, a random sample of subjects will be selected for a detailed audit of data items from high enrolling sites to determine acceptable error rates and will be used to drive clinical site staff re-training.

11.6 Good Clinical Practice

The study will comply with Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56 and 312.

12 Appendix

12.1 Vaccine Handling

See VERVE Investigator Brochure for Details

12.2 Informed Consent

See VERVE Informed Consent Form for full text

12.3 Case Report Forms

See appendix for paper and electronic mockups of case report forms. These will be converted to final electronic format once the study is initiated.

12.4 Call Script for Telephone Assessment of Primary Study Outcome

(Separate Appendix)

12.5 Manual of Operating Procedures

(Separate Appendix)

12.6 Sample Collection and Case Definition for Suspected Varicella Infection, with Dermatomal Map

13 Specimen Collection

At the time of presentation, lesions will be scraped for the detection of VZV DNA by polymerase chain reaction (PCR). Of note, PCR has replaced other diagnostic tests because of the enhance sensitivity and specificity; thus, it will be applied to lesions scrapings and/or scabs as collected.[36-37] Specimens from skin lesions are best collected by un-roofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of the skin lesion with a polyester swab. Scabs from healing skin lesions lacking vesicles are also optimal specimen types for PCR detection of VZV DNA (http://www.cdc.gov/vaccines/pubs/surv-manual/chpt17-varicella.html). Lesions will be scraped using a sterile disposable plastic curette. Instructions on performing this simple procedure will be included as part of site training on VERVE protocol that will be conducted via webcast prior to site initiation. The curette will be placed directly into a sterile test tube containing 0.5 ml of transport media (provided by the Coordinating Center). It will be coded with the patient's identification number and frozen at -20 up to -80 degrees C until shipped to the UAB VERVE Coordinating Center Biorepository.

Regarding blood collection, serum will be separated from whole blood following low-speed standard centrifugation, transferred to plastic cryovials and coded with the patient's identification number. The blood will be stored at -20 up to -80 degrees C until shipped with other specimens to the biorepository. The green top and purple top tubes will be shipped overnight at room temperature to the appropriate site for further processing.

13.1 Shipment of Specimens

The green top tubes for PBMCs, the purple top tubes for isolation of DNA, buffy coat and plasma and serum separate specimens in combo-boxes will be shipped overnight to the UAB Biorepository. Shipments will occur on all days of the week except Saturday or Sunday by express courier. The Coordinating Center and Biorepository will be informed electronically of the shipment (return receipt). Once received, all specimens will be bar coded and separated from those for PCR determinations versus those for the Biorepository.

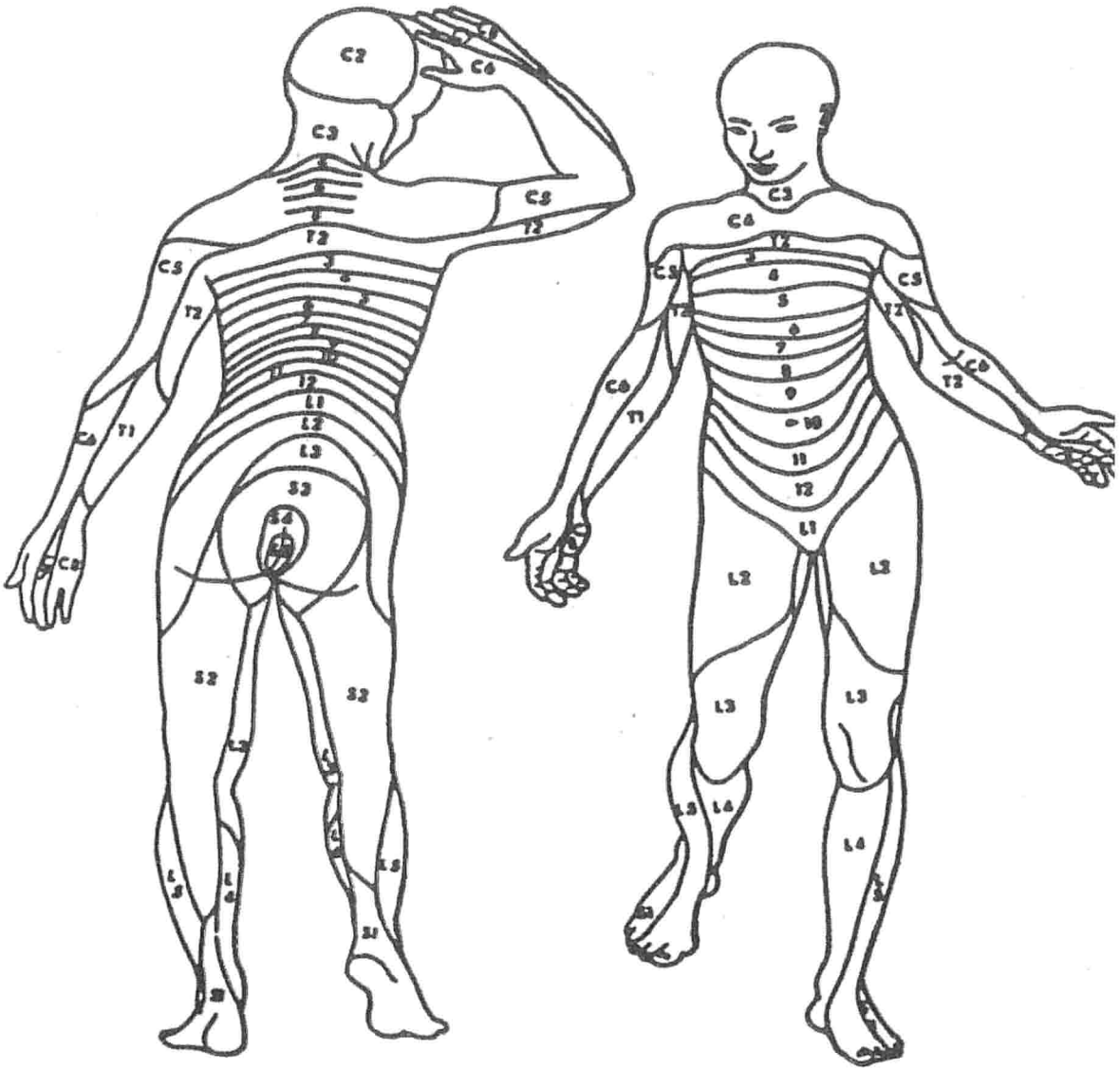
13.2 PCR Evaluation of Specimens

Lesion scrapings and scabs will be evaluated by PCR using three sets of primers for the detection of VZV, HSV, and a host cell β-globin gene sequence. These assays will be performed in the laboratory of Drs. Mark Prichard and Richard Whitley both of whom have generated years of experience in the detection of HSV and VZV DNA in diagnostic specimens. Briefly, DNA from swabs will be isolated using a Qiagen EZ1 Advanced XL instrument and the resulting DNA will be evaluated by a qualitative real time PCR assay. For VZV, forward primer 5'-TCT TGT CGA GGA GGC TTC TG-3', reverse primer 5'-TGT GTG TCC ACC GGA TGA T-3', and the probe 5'-(FAM)–TCT CGA CTG GCT GGG ACT TGC G-(TAMRA)-3' will amplify and confirm the presence of VZV DNA. Positive and negative controls will be included in each assay to ensure the performance of the experimental methods. To detect evidence of HSV DNA, primers will be used that detect both HSV-1 and HSV-2. Primers 5'-CAT CAC CGA CCC GGA GAG GGA C-3', 5'-GGG CCA GGC GCT TGT TGG TGT A-3', and the probe 5'-(FAM)–CCG CCG AAC TGA GCA GAC ACC CGC GC-(TAMRA)-3' will be used to detect the presence of HSV DNA. The assay will also include positive and negative controls monitor the performance of the assay. The β-globin controls are: 5'-CAA CTT CAT CCA CGT TCA CC and 5'-GAA GAG CCA AGG ACA GGT AC.

Distinguishing between vaccine and wild type zoster will be performed according to the method of Scott Schmid (CDC). The importance of detailed sequencing was recently emphasized.[37]

All results will be reported in real time to the Coordinating Center data base.

14 Dermatome Map



15 Summary of Changes

Protocol Number: VERVE

Protocol Title: The Safety and Effectiveness of the VaricElla zosteR VaccinE (VERVE) in Anti-TNF Users

	Version Number	Version Date
Current Approved Protocol	Version 1	2-28-2013
Amended Protocol	Version 2	10-30-2013
Amended Protocol	Version 3	07-31-2014
Amended Protocol	Version 4	09-04-2015
Amended Protocol	Version 5	03-04-2016
Amended Protocol	Version 6	07-13-2016
Amended Protocol	Version 7	09-25-2017
Amended Protocol	Version 8	08-28-2018

Section and page numbers are references to the *tracked changes version* of the amended protocol.

Amendment Version 2

1. ***3.1 Study Overview, Page 12***
   Old Text: All participants will have a one year telephone contact to assess for post-vaccination AEs.

   New Text: All participants will have a 6 month telephone contact to assess for post vaccination AEs. Patients that received the Zostavax injection will have an in clinic 1 year follow up blood draw.

   Rationale for Change: These are changes to comply with the FDA requested protocol that was approved.

2. ***3.4.4., Schedule of Study Visits, Page 16***
   Old Text: day 3, weekly until week 6, Phase 1 F/U Phone Call safety, 1 year.

   New Text: day 3, weekly until week 6 Phase I, 6 months and 1 year & in clinic blood draw.

Rationale for Change: These are changes to comply with the FDA requested protocol that was approved.

3. ***3.4.4., Schedule of Study Visits, Page 16***
   Old Text: Home Health F/U 500 VO

   New Text: Home Health F/U 500 VO (Not in ACR Pilot)

   Rationale for Change: The long-term one year home health follow-up visit is not included in the pilot grant of this protocol.

4. ***Administrative changes:*** Dates were updated to October 30, 2013, and version was changed from 1 to 2. Summary of Changes section 15 was added to protocol and section 16 was created and References were moved to this section.

Amendment Version 3

1. ***Title Page, title changed, page 1***
   Old Text: Safety and Effectiveness of the Live Zoster Vaccine in Anti-TNF Users (VERVE Trial)

   NEW Text: The Safety and Effectiveness of the VaricElla zosteR VaccinE (VERVE) in Anti-TNF Users Trial

2. ***1.2 Risk of Risk of Herpes Zoster in Patients with Rheumatoid Arthritis and Recommendations regarding Vaccination with the Live Zoster Vaccine, page 6***
   Old Text: Patients with rheumatoid arthritis (RA) are at an approximately 2-3 fold higher risk of HZ compared to the general population, making the prevention of HZ in this population a high priority.

   New Text: Patients with rheumatoid arthritis (RA) are at an approximately 2 fold higher risk of HZ compared to the general population, making the prevention of HZ in this population a high priority.

3. ***1.2 Risk of Risk of Herpes Zoster in Patients with Rheumatoid Arthritis and Recommendations regarding Vaccination with the Live Zoster Vaccine, page 7***

   Old Text: This recommendation was based solely upon expert opinion, as the vaccine (Zostavax®) had not been studied specifically in such individuals and absence of experimental or observational data.

   New Text: This recommendation was based solely upon expert opinion, as the vaccine (Zostavax®) had not been studied specifically in such individuals and there was a near-complete absence of experimental or observational data.

4. ***1.2 Risk of Risk of Herpes Zoster in Patients with Rheumatoid Arthritis and Recommendations regarding Vaccination with the Live Zoster Vaccine, page 7***

   Old Text: Similarly, this recommendation was based on expert opinion The American College of Rheumatology (ACR) endorsed this contraindication in its updated ACR 2012 recommendations for biologic and non-biologic disease modifying anti-rheumatic drug (DMARD) use in RA patients (developed by several of the study investigators including Drs. Curtis, Winthrop, and Saag), however this endorsement relied upon the ACIP recommendations and was not data-driven.

   New Text: The American College of Rheumatology (ACR) endorsed this contraindication in its ACR 2012 recommendations for biologic and non-biologic disease modifying anti-rheumatic drug (DMARD) use in RA patients (developed by several of the study investigators including Drs. Curtis, Winthrop, and Saag); however this endorsement echoed the ACIP recommendations and was not data-driven.

5. ***1.3.1 Potential Safety Concerns for Patients with Autoimmune Diseases, page 7***

   Old Text: The zoster vaccine was not administered to immunosuppressed participants in the large Shingles Prevention Study (SPS) 5; and potential participants with RA and other autoimmune diseases receiving immunosuppressive or immunomodulating agents including glucocorticoids and biologic and non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) were excluded.

   New Text: The zoster vaccine was not administered to immunosuppressed participants in the large Shingles Prevention Study (SPS) 5; potential participants with RA and other autoimmune diseases receiving immunosuppressive or immunomodulating agents including glucocorticoids and biologic and non-biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) were excluded from the pivotal trials of the vaccine.

6. ***1.3.1 Potential Safety Concerns for Patients with Autoimmune Diseases, page 8***

   Old Text: Further, there is some evidence to suggest that patients who use anti-TNF therapy are not at higher risk to develop HZ.

   New Text: Further, there is observational evidence to suggest that patients who use anti-TNF therapy are not at higher risk to develop HZ.

7. ***1.3.3 Zostavax® Safety among Biologic-exposed Patients with Autoimmune Diseases, page 9***

   Old Text: We have conducted a retrospective cohort study to examine the safety and effectiveness of zoster vaccine among Medicare beneficiaries diagnosed with RA or other immune-mediated diseases (psoriatic arthritis, psoriasis, ankylosing spondylitis, or inflammatory bowel disease).

New Text: We conducted a retrospective cohort study to examine the safety and effectiveness of zoster vaccine among Medicare beneficiaries diagnosed with RA or other immune-mediated diseases (psoriatic arthritis, psoriasis, ankylosing spondylitis, or inflammatory bowel disease).

8. ***1.3.3 Zostavax® Safety among Biologic-exposed Patients with Autoimmune Diseases, page 9***

Old Text: Adjusting for demographics, type of immune-mediated disease, health care utilization, and exposure to biologic and non-biologic DMARDs and oral glucocorticoids, zoster vaccine was associated with a 39% reduction in the rate of HZ infection (adjusted hazard ratio 0.61 [95% CI; 0.52-0.71]). The receipt of the zoster vaccine was effective and associated with similar reductions in HZ risk and subsequent post-herpetic neuralgia as that observed in the SPS.

New Text: Adjusting for demographics, type of immune-mediated disease, health care utilization, and exposure to biologic and non-biologic DMARDs and oral glucocorticoids, zoster vaccine was associated with a 39% relative reduction in the rate of HZ infection (adjusted hazard ratio 0.61 [95% CI; 0.52-0.71]). The receipt of the zoster vaccine was effective and associated with similar absolute reductions in HZ risk and subsequent post-herpetic neuralgia as that observed in the SPS.

9. ***1.3.3 Zostavax® Safety among Biologic-exposed Patients with Autoimmune Diseases, page 10***

Old Text: Although it might be possible to discontinue biologic treatments for at least 1-2 months, vaccinate and then restart biologic therapy one to two months following vaccination, our findings suggest that this strategy is rarely employed. This may be due to concern regarding a flare in RA disease while off biologic therapy for the prolonged time-period necessary to vaccinate (likely), making this practice unacceptable to many patients and their physicians.

New Text: Although it might be possible to discontinue biologic treatments for at least 1-2 months (to facilitate drug washout), vaccinate and then restart biologic therapy approximately one month following vaccination, our findings suggest that this strategy is rarely employed,. This may be due to concern regarding a flare in RA disease while off biologic therapy for the prolonged time-period necessary to vaccinate, making this practice unacceptable to many patients and their physicians.

10. ***2.1 Primary Objectives and endpoint, page 11***

Old Text: To evaluate vaccine immunogenicity by measuring VZV-specific T cell responses (correlates of HZ immunoprotection) and VZV glycoprotein-specific (gp-specific) antibody titers (used as surrogate outcomes in the prior SPS 1).We hypothesize

that patients using anti-TNF therapies who receive the live zoster vaccine will be able to achieve a greater increase in the VZV-specific T cell response measured 6 weeks post vaccination compared to patients using anti-TNF therapies receiving placebo vaccine.

New Text: To evaluate vaccine immunogenicity by measuring VZV-specific T cell responses (correlates of HZ immunoprotection) and VZV glycoprotein-specific (gp-specific) antibody titers (used as surrogate outcomes in the prior SPS trial).We hypothesize that patients using anti-TNF therapies who receive the live zoster vaccine will be able to achieve a greater increase in the VZV-specific T cell response measured 6 weeks post vaccination compared to patients using anti-TNF therapies receiving placebo

11. ***2.2 Secondary Objectives and endpoints, page 11***

Old Text: To estimate the clinical effectiveness of the HZ vaccine in reducing longer-term HZ risk. Incident HZ cases occurring up to 2 years following vaccination and beyond will be ascertained among enrollees in Medicare or a large commercial health plans (e.g. WellPoint, comprising Blue Cross / Blue Shield plans in 14 U.S. states) using a novel linkage to administrative health plan data. We will examine longer-term reduction in risk for herpes zoster and the potential for decreased vaccine effectiveness over time to prevent HZ, which might suggest waning immunity and the need for re-vaccination. This outcome will be ascertained using administrative claims data among the majority of VERVE participants who are linkable to the health plan data sources available to the trial.

New Text: To evaluate vaccine immunogenicity by measuring VZV-specific T cell responses (correlates of HZ immunoprotection) and VZV glycoprotein-specific (gp-specific) antibody titers (used as surrogate outcomes in the prior SPS trial).We hypothesize that patients using anti-TNF therapies who receive the live zoster vaccine will be able to achieve a greater increase in the VZV-specific T cell response measured 6 weeks post vaccination compared to patients using anti-TNF therapies receiving placebo

12. ***3.1 Study Design, 12***

Old Text: Phase I patients, consisting of the first 250 individuals recruited, will have three in-clinic visits, one at screening, randomization and again at 6 weeks follow-up. Blood samples will be drawn at two visits and additional safety data from at-home patient diaries will be collected from these participants. Participants will be contacted by telephone three (3) days after receiving either Zostavax® or Placebo and then every week until their 6 weeks in-office follow up visit to remind participants to complete the vaccine report card (diary), to check for early post-vaccination AEs and as a reminder to notify their study contact for changes in health status that might indicate VZV disease (such as rash). All participants will have a 6 month telephone contact to assess for post-

vaccination AEs. Patients that received the Zostavax injection will have an in clinic 1 year follow up blood draw.

Phase II participants (750 individuals) will be screened, and if eligible, consent to participate and randomized on the same day to receive either Zostavax® or placebo (saline) injection. Phase II participants will have two in-clinic visits at screening/randomization and at six weeks unless an unscheduled visit is needed. All participants will have a one year telephone contact to assess for post-vaccination AEs and SAEs.

For all participants who are enrolled in a health plan with data that can be linked to VERVE (e.g. Medicare), effectiveness follow-up will continue for at least 3 years after randomization and will rely on linked administrative claims data from Medicare. Patients will be consented for this linkage and to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information.

New Text: All patients will have two in-clinic visits, one at screening/randomization (a single visit) and again at 6 weeks follow-up. Blood samples will be drawn at these visits and additional safety data from at-home patient diaries will be collected from these participants. Participants will be contacted by telephone three (3) days after receiving either Zostavax® or Placebo and then every week until their 6 weeks in-office follow up visit to remind participants to complete the vaccine report card (diary), to check for early post-vaccination AEs and as a reminder to notify their study contact for changes in health status that might indicate VZV disease (such as rash). All participants will have a 6 month telephone contact to assess for post-vaccination AEs. Patients that received the Zostavax injection and agree will have a follow-up visit at 1 year post randomization for blood draw and clinical data collection. Conditional on future funding, patients will be contacted annually for up to ten years.

For all participants who are enrolled in a health plan with data that can be linked to VERVE (e.g. Medicare), effectiveness follow-up will be assessed after randomization and will rely on linked administrative data (medical, pharmacy claims). Patients will be consented for this linkage and sign a HIPAA authorization to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information, including linkage with health plan data. The duration of follow-up in health plan data is expected to be at least one year. Conditional on future funding, more extended follow-up is anticipated using this method, up through ten years.

13. ***3.2 Data Collections for Phase 1, pages 12-13***

Old Text: Initially, Phase I will recruit 50 patients at the University Alabama Birmingham (UAB) and 50 patients at Oregon Health and Science University (OHSU) rheumatology clinics who are being treated with anti-TNF therapy with or without DMARDs, and test positive for Varicella IgG. For these first 100 patients, and consistent with the FDA guidance provided during our pre-IND meetings with FDA, any patients having received any parenteral or oral corticosteroids in the last 30 days, will be excluded. Data on the

occurrence of rash or other local or systemic symptoms suggestive of VZV infection from day 0 to day 42 following vaccination will be collected (see below). These data will be collected at the 6-week, in-person follow-up visit, as well as via at-home patient diaries (vaccine patient report card) filled out during this 42 day interval. To facilitate this data collection, these Phase I participants will be provided with an at-home paper diary to record AEs. The diary will collect information about injection site reactions, and other AEs using methods similar to the SPS trial.5 Subjects will also be asked to provide information regarding RA disease activity and flare. This diary will be reviewed at the 6 week in-person visit. Additionally, patients will be prompted at baseline to promptly report any AEs or SAEs that occur within the first 42 days to their study physician as soon as they may occur. They will also receive once weekly phone calls from study site nurses at UAB and OHSU to prompt for information regarding AEs and SAEs of interest. Any symptom suggestive of an SAE or a VZV event (e.g. new painful skin rash, constitutional symptoms such as fever, other symptoms in the skin and subcutaneous tissue MEDRA category) will trigger the need for the patient to return for an in-person safety visit.
Assuming that no serious safety concerns are identified, Phase I will continue and recruit an additional 150 patients between UAB, OHSU and at select clinical sites if needed. The prohibition against use of recent or current glucocorticoid therapy will be dropped, and patients may be included if they have received prednisone-equivalent doses of up to 10 mg per day, as long as the dose has been stable for the last 30 days.

New Text: Initially, Phase Ia will recruit 50 patients at the University Alabama Birmingham (UAB) and 50 patients at Oregon Health and Science University (OHSU) rheumatology clinics who are being treated with anti-TNF therapy with or without DMARDs, and who test positive for Varicella IgG. Varicella IgG status must be known at or prior to randomization and may be used as long as it is verified as positive within one year prior to randomization. For these first 100 patients, and consistent with the FDA guidance provided during our pre-IND meetings with FDA, any patients having received any parenteral or oral corticosteroids in the last 30 days will be excluded. Following randomization, data on the occurrence of rash or other local or systemic symptoms suggestive of VZV infection from day 0 to day 42 following vaccination will be collected (see below). These data will be collected at the 6-week, in-person follow-up visit, as well as via at-home patient diaries (vaccine patient report card) filled out during this 42 day interval. To facilitate this data collection, these Phase Ia participants will be provided with an at-home paper diary to record AEs. The diary will collect information about injection site reactions, and other AEs using methods similar to the SPS trial.5 Subjects will also be asked to provide information regarding RA disease activity and flare. This diary will be reviewed at the 6 week in-person visit. Additionally, patients will be prompted at baseline to promptly report any AEs or SAEs that occur within the first 42 days to their study physician as soon as they may occur. They will also receive once weekly phone calls from study site nurses at UAB and OHSU to prompt for information regarding AEs and SAEs of interest. Any symptom suggestive of an SAE or a VZV event (e.g. new painful skin rash, constitutional symptoms such as fever, other symptoms in the skin and

subcutaneous tissue MEDRA category) will trigger the need for the patient to return for an in-person safety visit.

Assuming that no serious safety concerns are identified, Phase I will continue and recruit an additional 150 patients between UAB, OHSU and at select clinical sites if needed (Phase 1b of the trial). For these additional 150 patients, confirmation of varicella IgG status must be known, as described above. However, the prohibition against use of recent or current glucocorticoid therapy will be dropped, and patients may be included if they have received prednisone-equivalent doses of up to 10 mg per day, as long as the dose has been stable for the last 30 days.

14. ***3.3 Phase II, Page 3,4***

Old Text: The second phase will enroll 750 patients from additional academic and community sites. The eligibility criteria are the same with those from the end of the Phase I study, but with the removal of the positive VZV test criteria. Safety data that will support the primary outcome of the trial will be collected via a scheduled in-clinic 6 weeks and one year after vaccination phone call, although patients will also be instructed to report any AEs suggestive of a VZV event and any SAEs that occur within the first 42 days promptly to their study physician and return for an in-person visit as soon as they may occur.

New Text: The second phase of the trial will enroll 750 patients from additional academic and community sites. The eligibility criteria are the same with those from the end of the Phase I study, but with the removal of the positive VZV test criteria. Safety data that will support the primary outcome of the trial will be collected via a scheduled in-clinic visit 6 weeks after vaccination and a 6 month phone call. Patients will also be instructed to report any AEs suggestive of a VZV event and any SAEs that occur within the first 42 days promptly to their study physician and return for an in-person visit as soon as they may occur.

15. ***3.4.1 Inclusion Criteria, page 14***

Old Text:

- Must be 50 years of age or older
- Must be currently treated with an anti-TNF therapy at the time of vaccination. Specifically, most recent weekly etanercept dose must have occurred within 7 days, most recent adalimumab dose must have occurred within 14 days, most recent certolizumab dose must have occurred within 14 days, most recent golimumab dose must have occurred within 30 days, and most recent infliximab infusion must have occurred within 56 days.
- Diagnosis of RA or another inflammatory arthritis
- The first 250 patients recruited to Phase I must test positive for VZV IgG.
- Subjects should have a self-reported history of prior varicella infection (i.e. chicken pox) or long-term residence (>30 years) in the continental US.

- The first 100 patients recruited to phase I must not have received any oral or systemic glucocorticoids within 30 days prior to vaccination. Intra-articular glucocorticoid injections within the previous 30 days are acceptable.
- Subjects should be on stable doses of all biologic and non-biologic DMARDs for a minimum of 30 days prior to vaccination.
- Eligible women must be post-menopausal (> 1 year since last menstrual period) or have a surgical history of bilateral oophorectomy or hysterectomy.
- Subjects should be ambulatory, community dwelling and capable of giving informed consent.

New Text:

- Must be 50 years of age or older
- Must be currently treated with an anti-TNF therapy at the time of vaccination. Specifically, most recent weekly etanercept dose must have occurred within 7 days, most recent adalimumab dose must have occurred within 14 days, most recent certolizumab dose must have occurred within 14 days, most recent golimumab dose must have occurred within 30 days, and most recent infliximab infusion must have occurred within 56 days.
- Diagnosis of RA or another inflammatory arthritis
-
- The first 250 patients recruited to Phase I must test positive for VZV IgG.
- Subjects should have a self-reported history of prior varicella infection (i.e. chicken pox) or long-term residence (>30 years) in the continental US.
- The first 100 patients recruited to phase I must not have received any oral or systemic glucocorticoids within 30 days prior to vaccination. Intra-articular glucocorticoid injections within the previous 30 days are acceptable.
- Subjects should be on stable doses of all biologic and non-biologic DMARDs for a minimum of 30 days prior to vaccination.
- Eligible women must be post-menopausal (> 1 year since last menstrual period) or have a surgical history of bilateral oophorectomy or hysterectomy.
- Subjects should be ambulatory, community dwelling and capable of giving informed consent.

16. ***3.4.2 Exclusion Criteria***

Old Text:

Patients will be excluded if they meet any of the following exclusion criteria

- Prior use of the zoster vaccine (Zostavax®, Merck)
- Glucocorticoids at a prednisone-equivalent daily dose > 10mg/day
- Any known contraindication to Zostavax® vaccine, including allergy or sensitivity to gelatin or any other vaccine component
- Known HIV/AIDS
- Currently receiving radiation or chemotherapy for any type of malignancy

- Any current use (within the last 30 days) of acyclovir, valacyclovir, or famciclovir
- Receipt of any other immunizations within one month before study vaccination (2 weeks in the case of inactivated influenza vaccines or other non-replicating immunization products [e.g., dT, pneumococcal vaccine, hepatitis A vaccine, hepatitis B vaccine]), or scheduled within 6 weeks after recruitment.
- Active infection or inter-current illness (e.g., urinary tract infection, influenza)
- Participated in an investigational study within 1 month prior to study entry
- Active drug or alcohol use, dependence, or any other reason that, in the opinion of the site investigator, would interfere with the study
- Significant underlying illness that would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 3 years)
- Any other reason that, in the opinion of the site investigator, would interfere with required study related evaluations (e.g. uncontrolled comorbidity, life expectancy < 1 year) Patients who have household contact with varicella-susceptible pregnant women or severely immunosuppressed individuals without history of primary varicella.

New Text:

Patients will be excluded if they meet any of the following exclusion criteria

- Prior use of the zoster vaccine (Zostavax®, Merck)
- Glucocorticoids at a prednisone-equivalent daily dose > 10mg/day (for Phase 1b and Phase II participants; all systemic glucocorticoid use is prohibited for Phase 1a patients)
- Any known contraindication to Zostavax® vaccine, including allergy or sensitivity to gelatin or any other vaccine component
- Known HIV/AIDS
- Currently receiving radiation or chemotherapy for any type of malignancy
- Any current use (within the last 30 days) of acyclovir, valacyclovir, famciclovir, or foscarnet
- Receipt of any other immunizations within one month before study vaccination (2 weeks in the case of inactivated influenza vaccines or other non-replicating immunization products [e.g., dT, pneumococcal vaccine, hepatitis A vaccine, hepatitis B vaccine]), or scheduled within 6 weeks after recruitment.
- Active infection or inter-current illness (e.g., urinary tract infection, influenza)
- Participated in an investigational study within 1 month prior to study entry

- Active drug or alcohol use, dependence, or any other reason that, in the opinion of the site investigator, would interfere with the study
- Significant underlying illness that would be expected to prevent completion of the study (e.g., life-threatening disease likely to limit survival to less than 3 years)
- Any other reason that, in the opinion of the site investigator, would interfere with required study related evaluations (e.g. uncontrolled comorbidity, life expectancy < 1 year)
- Patients who have household contact with varicella-susceptible pregnant women or severely immunosuppressed individuals without history of primary varicella.

17. *3.4.4 Schedule of Study Visits*

Old Diagram & Text:

Activity per Protocol	Phase I Office Visits (250)			Phase II Office Visit and Home Health Visit (750)		Phase I & II Follow Up Visits			
Visits*	#1 Screen	#2 Rand	#3 F/U	#1 Screen, Rand	#2 F/U	F/U Phone Call Safety	Home Health F/U 500 VO (Not in ACR Pilot)	F/U via Claims Data	Unsch
Visit Time (Weeks/Years)		Wk 0	Wk 6	Wk 0	Wk 6	day 3, weekly until week 6 Phase I, 6 months and 1 year & in clinic blood draw. (	Year 1	Year 3	As Needed
Informed Consent	X			X					
Inclusion/Exclusion Criteria (Eligibility)	X			X					
Vital Signs	X	X	X	X	X				X
Baseline Demographics	X			X					
Screening Questionnaire	X			X					
CDAI	X	X	X	X	X				
RAPID3	X	X	X	X	X				
ELISPOT (For VZV IgG, 1 SST)	X								
Zostavax Vaccine		X		X					
Immunogenicity Sub Study (PBMC, gp-Elisa) 2 green top at screening (250 in Phase I; 750 in Phase II; 500 vaccinated at 1 years	X (250)		X (250)	X (750)	X (750)		X (500)		
UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma	X			X					
Randomization & Study Medication Administration unblinded	X			X					
Post vaccination Rash-Doctors Office as Needed									X
Safety Telephone Call						X (1000)			
Records request to confirm HZ and/or PHN			X		X	X			X
1 Year blood draw for						X			

patients that were given Zoster Vaccine									
Outcomes assessment via Medical claims data with medical record confirmation								X	
Photograph/Swab for PCR lesions & scabs as needed to UAB									X
Concomitant Medication	X	X	X	X	X	X			X
Adverse Events	X	X	X	X	X	X			X

[+]Phase I refers to the first 250 patients; Phase II refers to the remaining 750 patients

New Diagram & Text:

Activity per Protocol	Phase I Office-Based n=250 patients			Phase II Office-Based n=750 patients		Phase I & II Follow Up Visits			
Visits	#0 Screen*	#1 Baseline	#2 F/U	#1 Baseline	#2 F/U	F/U Phone Call Safety	Extended F/U 500 VO[†]	F/U via Claims Data	Unsch
Visit Time (Weeks/Years)		Wk 0	Wk 6***	Wk 0	Wk 6***	Phase I: day 3, weekly until week 6 Phase I and II: 6 months	Year 1 & annually for 10 years**	long-term**	As Needed
Informed Consent	X			X					
Inclusion/Exclusion Criteria (Eligibility)	X			X					
Vital Signs		X	X	X	X				X
Baseline Demographics		X		X					
Screening Questionnaire		X		X					
CDAI		X	X	X	X				
RAPID3		X	X	X	X				
ELISPOT (For VZV IgG, 1 SST)	X								
Zostavax Vaccine/Placebo		X		X					
Immunogenicity (PBMC, gp-Elisa) 2 green top at screening (250 in Phase I; 750 in Phase II; all 500 vaccinated pts, annually		X (250)	X (250)	X (750)	X (750)		X (500)		
UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma		X	X	X	X				
Randomization & Study Medication Administration unblinded		X		X					
Post vaccination Rash-Doctors Office as Needed									X
Safety Telephone Call						X (1000)			
Records request to confirm HZ and/or PHN			X		X	X			X
Annual clinical assessment & blood draw for patients that were given Zoster Vaccine							X		
Outcomes assessment via claims data with possible medical record								X	

confirmation									
Photograph/Swab for PCR lesions & scabs as needed to UAB									X
Concomitant Medication		X	X	X	X	X			X
Adverse Events		X	X	X	X	X			X

Note: Phase I refers to the first 250 patients; Phase II refers to the remaining 750 patients
* no explicit in-person screening visit is required; VZV lab testing is expected to be accommodated at a standard of care visit ** Conditional on future funding *** A 2 week window after 6 weeks is permissible (i.e. visit may occur 6-8 weeks after randomization)
† Visit will be made at a venue other than study sites (e.g. phone-based contact with bio-specimen collection)

18. ***3.4.5 Screening, page 17***

Old Text: Patients will be screened using screening questions provided to each site that have been developed for the study. Simple screening questions will focus on whether the potential participant is a current user of one of the five approved anti-TNF therapies. Screening questions are shown in paper CRF mockups in the Appendix. For qualifying patients, the diagnosis of RA/PSA, use of anti-TNF therapy and oral glucocorticoids, and other information regarding the inclusion/exclusion criteria will be validated by the physician. The physician will also be available to answer any question relating to the study procedures. Basic demographic information that is de-identified will be requested for those who fail the screening.

New Text: At the randomization visit, patients will be screened using screening questions. Simple screening questions will focus on whether the potential participant is a current user of one of the five approved anti-TNF therapies. Screening questions are shown in paper CRF mockups in the Appendix. For qualifying patients, the diagnosis of RA/PSA, use of anti-TNF therapy and oral glucocorticoids, and other information regarding the inclusion/exclusion criteria will be confirmed by the physician. The physician will also be available to answer any question relating to the study procedures. Basic demographic information that is de-identified will be requested for those who fail the screening or refuse consent. For factors that represent temporary exclusions (e.g. dose of background DMARDs not stable for > 30 days), rescreening at a later date is permitted without any limitations.

19. ***3.4.6 Informed Consent, page 17***

Old Text: As part of this process, participants will be asked to provide consent to link study-related data to administrative data (e.g. Medicare) and to sign a generic release of information for future procurement of medical records related to study outcomes in the event these are needed.

New Text: As part of this process, participants will be asked to provide consent to link study-related data to administrative data (e.g. Medicare) and to sign a generic release of information and a HIPAA authorization for future procurement of medical records related to study outcomes in the event these are needed.

20. ***3.4.8 Blinding***

Old Text: However, Zostavax® cannot be blinded without a substantial commitment by the manufacturer (Merck). Therefore, each site will have an un-blinded nurse who is able to give the vaccine or placebo (saline) injection in an opaque syringe. The un-blinded nurse is required to be independent of the study and is not a member of the sponsoring organization. Blinding will be maintained at least for 42 days after vaccination at which time the primary outcome (safety) is assessed.

New Text: However, Zostavax® cannot be blinded without a substantial commitment by the manufacturer (Merck), who is not willing to provide this commitment. Therefore, each site will have an un-blinded nurse who is able to give the vaccine or placebo (saline) injection in an opaque syringe. The un-blinded nurse is required to be independent of the study and is not a member of the sponsoring organization. Blinding will be maintained at least for 42 days after vaccination at which time the primary outcome (safety) is assessed. Blinding is expected to continue through the 6 month phone visit. All patients are expected to be unblinded after the 6 month visit but before 12 months. For patients who were vaccinated (but not those who received vaccine), they will subsequently undergo unblinded annual follow-up for clinical assessment (e.g. occurrence of herpes zoster-related events) and immunologic assessment.

21. ***4.1.1 Serious Adverse Event Collection and Reporting, page 23***

Old Text: Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

New Text: Following the subject's written consent to participate in the study and randomization, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures.

22. ***4.2.1 Non Serious Adverse Event Collection and Reporting, page 24***

Old Text: The collection of non-serious AE information should begin at initiation of study.

New Text: The collection of non-serious AE information should begin at initiation of study drug and will extend through the 6 week follow-up visit. No AE reporting beyond the 6 week visit is required.

23. ***4.3.2 Procedures for Reporting and Recording, Page 27***

Old Text: All suspect vaccine-strain VZV cases will be evaluated while maintaining the study blind. For any rash with or without pain that develops within the 6 weeks following vaccination, participants will be instructed to immediately contact the site physician for evaluation and also contact the UAB Coordinating Center. Sites also will be instructed to take photos of the rash using the study provided camera or smartphone camera and will collect biologic specimens (lesion swab, collected according to the Manual of Operating Procedures).

New Text: All suspected vaccine-strain VZV cases will be evaluated while maintaining the study blind. For any rash with or without pain that develops within the 6 weeks following vaccination, participants will be instructed to immediately contact the site physician for evaluation and also contact the UAB Coordinating Center. Sites also will be instructed to take photos of the rash and will collect biologic specimens (lesion swab, collected according to the Manual of Operating Procedures).

24. ***4.3.2 Procedures for Reporting and Recording, Page 28***

Old Text: Therefore, these cases will be included in the outcome events analyzed for the primary outcome, but excluded as part of a sensitivity analysis that will be reported as a secondary endpoint of the trial.

New Text: Therefore, these cases will be included in the outcome events analyzed for the primary outcome, assuming they are adjudicated as probable or confirmed following clinical adjudication. They will be excluded as part of a sensitivity analysis that will be reported as a secondary endpoint of the trial of PCR-confirmed vaccine-strain VZV events.

25. ***4.3.4 SAE Follow-up, page 28***

Old Text: All SAEs that are encountered during the protocol-specified AE reporting period should be actively followed to their resolutions, or until the investigator assesses them as stable, or the subject is lost to follow-up.

New Text: All SAEs that are encountered during the protocol-specified AE reporting period (i.e. through 6 months) should be actively followed to their resolutions, or until the investigator assesses them as stable, or the subject is lost to follow-up.

26. ***4.3.4 SAE Follow-up***

Old Text: SAEs may be followed up by telephone, fax, electronic mail, and/or additional visit(s) to obtain additional case details deemed necessary to appropriately evaluate the SAE report. For the first 250 patients recruited into Phase I of the study, the study site personnel will be responsible for obtaining hospital medical records and other relevant primary data. For the remaining 750 patients, the VERVE Call Center will have primary responsibility for obtaining hospital medical records if the patient has been hospitalized

and any additional medical record data that has not been directly collected by the site personnel.

SAEs can be reported spontaneously at any point during the first 42 days after receipt of the vaccine injection. All participants will be evaluated in person (Phase I participants, first 250) or via telephone (remaining 3750participants) to prompt them to report any SAEs or previously unreported rash or symptoms consistent with varicella infection.

New Text: SAEs may be followed up by telephone, fax, electronic mail, and/or additional visit(s) to obtain additional case details deemed necessary to appropriately evaluate the SAE report. Medical records for events occurring between the baseline and 6 week follow-up visits will be obtained by study sites. If medical records cannot be obtained by study sites for events occurring within these 6 weeks, and for all events occurring after the 6 week visit, the VERVE-assigned Call Center will have primary responsibility for obtaining medical records. This will include hospital records if the patient has been hospitalized and any additional medical record data needed that has not been directly collected by the site personnel.

SAEs can be reported spontaneously at any point during the first 42 days after receipt of the vaccine injection.

27. *5.1 Definition, page 29*

Old Text: Incident HZ cases occurring more than 42 days following vaccination will be identified from administrative claims data by the first HZ diagnosis code occurring during follow-up (ICD-9-CM code 053 and ICD 10 diagnosis code B02 beginning 2013) during hospitalization or physician office visit that was accompanied by a pharmacy claim for anti-viral treatment (acyclovir, famciclovir, valacyclovir) within +-7 days.

New Text: Incident HZ cases occurring more than 42 days following vaccination will be identified from administrative claims data by the first HZ diagnosis code occurring during follow-up (ICD-9-CM code 052.* (chickenpox), 053.* (herpes zoster), and ICD 10 diagnosis code B02 beginning 2014 during hospitalization or a physician office visit that was accompanied by a pharmacy claim for anti-viral treatment (acyclovir, famciclovir, valacyclovir) within +-7 days.

28. *5.1 Definition, page 29*

Old Text: The clinical implications of this secondary aim are to inform the potential need for re-vaccinating patients some years after initial vaccination.

New Text: The clinical implications of this secondary aim are to inform the potential need for re-vaccinating patients some years after initial vaccination. These data will also be used to assess the generalizability of the study population enrolled in the trial.

29. ***5.1 Definition, page 30***

Old Text: Although unlikely, herpes zoster (i.e. reactivation of varicella unrelated to vaccination) could also present during this time-period either as local or disseminated disease.

New Text: Although unlikely, herpes zoster (i.e. reactivation of varicella unrelated to vaccination) or primary infection could also present during this time-period either as local or disseminated disease.

30. ***5.1 Definition, page 30***

Old Text: Tolerability of vaccination using patient diaries (first 250 patients, collected at 6 week in-person visit)

New Text: Tolerability of vaccination using patient diaries (Phase I, first 250 patients, using data collected at 6 week in-person visit)

31. ***5.2 Procedures for Reporting and Recording Secondary Endpoints, page 30***

Old Text: Procedures for Reporting and Recording Secondary Endpoints

New Text: Additional Procedures for Reporting and Recording Endpoints

32. ***5.2.1 Lab-based Outcome Measures, page 30***

Old Text: Lab-based Outcome Measures
The secondary endpoints of the study include mechanistic studies to evaluate vaccine immunogenicity using surrogate measures of vaccine effectiveness including VZV gp-specific antibody titers and VZV-specific T cell responses

New Text: **Lab-based Outcome Measures (primary endpoint)**

Endpoints of the study include mechanistic studies to evaluate vaccine immunogenicity using surrogate measures of vaccine effectiveness including VZV gp-specific antibody titers and VZV-specific T cell responses.

33. ***5.3 Long-term Clinical Effectiveness – Ascertainment of Herpes Zoster Beyond 42 Days (Secondary endpoint)***

Old Text: Incident HZ cases beyond 6 weeks following vaccination will be identified from claims data by the first HZ diagnosis code occurring during follow-up (ICD-9-CM code 053 and 0.52x and ICD 10 diagnosis code B01.x and B02 beginning 2013) in an inpatient or physician office visit claim that was accompanied by a pharmacy claim for anti-viral treatment (acyclovir, famciclovir, valacyclovir) within 7 days before or after.

New Text: Incident HZ cases beyond 6 weeks following vaccination will be identified from claims data by the first HZ diagnosis code occurring during follow-up (ICD-9-CM code 053 and 0.52 and ICD 10 diagnosis codes beginning 2014) in an inpatient or physician office visit claim that was accompanied by a pharmacy claim for anti-viral treatment (acyclovir, famciclovir, valacyclovir) within 7 days before or after.

34. ***6.2 Primary Outcome (SA1): Immunogenicity***

Old Text: Samples for gp-ELISA measurements will be collected at the same 0 and 6 week time points and also at one year and evaluated at UCR based on the data from the SPS study.

New Text: Samples for gp-ELISA measurements will be collected at the same 0 and 6 week time points and also annually and evaluated at UCR based on the data from the SPS study.

35. ***6.3 Secondary Outcomes (SA2, SA3): Efficacy at 2 years and safety at 42 days, page 33***

Old Text: 6.3 Secondary Outcomes (SA2, SA3): Efficacy at 2 years and safety at 42 days

New Text: 6.3 Secondary Outcomes (SA2, SA3): Clinical effectiveness and safety

36. ***6.3 Secondary Outcomes (SA2, SA3): Efficacy at 2 years and safety at 42 days, page 33***

Old Text: For SA2 (longer term effectiveness of vaccination), and examining the risk of HZ and PHN after 6 weeks following vaccination, cumulative event rates for each outcome will be calculated as the project-limit estimates and a log-rank test will be used to assess whether the cumulative event rates for the vaccine and place groups differ.

New Text: For SA2 (longer term effectiveness of vaccination), and examining the risk of HZ and PHN after 6 weeks following vaccination, cumulative event rates for each outcome will be calculated as the product-limit estimator and a log-rank test will be used to assess whether the cumulative event rates for the vaccine and place groups differ.

37. ***6.3 Secondary Outcomes (SA2, SA3): Efficacy at 2 years and safety at 42 days, page 33***

Old Text: Because HZ risk is associated with the use of immunosuppressive agents for RA treatment, changes in their treatment regimen, e.g., discontinuing anti-TNF therapies, switching to other agent(s) may increase or decrease their HZ risk.

New Text: Because HZ risk is associated with the use of immunosuppressive agents, changes in patients' treatment regimen, e.g., discontinuing anti-TNF therapies, switching to other agent(s) may increase or decrease their HZ risk.

38. ***6.4. Statistical Methods***

Old Text: Baseline comparability will be assessed [parametric and nonparametric one factor (treatment group) analysis of variance] and examination of the correlates of Rheumatoid Arthritis disease history (Pearson or Spearman rank correlations) will be investigated.

New Text: Baseline comparability will be assessed [parametric and nonparametric one factor (treatment group) analysis of variance] and examination of the correlates of disease history (Pearson or Spearman rank correlations) will be investigated.

39. ***6.4.1 Primary Outcome***

Old Text: In addition, age adjusted and other covariate adjusted models will be assessed using both the 6 week and 1 year time points using an analysis of covariance model (ANCOVA) that included the log transformed VZV specific response as the response variable and treatment or subgroup as independent variables. In addition to age, other covariates considered will be sex, time point(s) after vaccination, immune responses at baseline, duration of RA, and type of RA medication.

New Text: In addition, age adjusted and other covariate adjusted models will be assessed using an analysis of covariance model (ANCOVA) that included the log transformed VZV-specific response as the response variable and treatment or subgroup as independent variables. In addition to age, other covariates considered will be sex, time point(s) after vaccination, immune response at baseline, and specific anti-TNF medication.

40. ***6.4.2 Secondary Outcomes***

Old Text: For the secondary outcomes, we will compare the proportion of participants experiencing SAEs and vaccine-strain VZV-like infections occurring during the first 42 days and at 2 years after vaccination.

New Text: For the secondary outcomes, we will compare the proportion of participants experiencing SAEs and vaccine-strain VZV-like infections occurring during the first 42 days and at later time points after vaccination.

41. ***6.5.1 Stopping Rules for Confirmed Vaccine-Strain VZV Cases, page 37***

Old Text: The study will be evaluated after the first 100 and 250 participants have been enrolled. Given that the expected rates of confirmed vaccine-strain VZV cases would be low (1 in 1000 participants), the trial will be stopped if 3 vaccine-strain VZV cases occur in the first 100 vaccinated participants (with at least 2 being in the active vaccine group) or 5 in the first 250 participants (with at least 3 being in the active vaccine group).

New Text: The study will be evaluated after the first 100 and 250 participants have been enrolled. Given that the expected rates of confirmed vaccine-strain VZV cases would be low (1 in 1000 participants), the trial will be stopped if 3 vaccine-strain confirmed VZV cases occur in the first 100 vaccinated participants (with at least 2 being in the active vaccine group) or 5 in the first 250 participants (with at least 3 being in the active vaccine group).

42. ***8 DSMB Governance, page 39***

Old Text: An independent Data and Safety Monitoring Committee (DSMB), comprised of members without conflicts of interest with the VERVE study, will be formed for this trial. The 5-member DSMB will include two infectious disease physicians with expertise in virology, an epidemiologist, a statistician, and a rheumatologist. The DSMB will be responsible for evaluating scientific issues related to the study. The DSMB will remain un-blinded to treatment allocation when monitoring adverse events.

The DSMB will receive data periodically (e.g. quarterly) including pre-specified time points including after the first 100 patients, the first 250 patients, and quarterly for the remaining 3750 patients.

New Text: An independent Data and Safety Monitoring Committee (DSMB), comprised of members without conflicts of interest with the VERVE study, will be formed for this trial. The 5-member DSMB is exposed to have a composition that includes infectious disease physicians with expertise in virology, an epidemiologist, a statistician, and a rheumatologist. The DSMB will be responsible for evaluating scientific issues related to the study. The DSMB will remain un-blinded to treatment allocation when monitoring adverse events.

The DSMB will receive data periodically (e.g. quarterly) including pre-specified time points including after the first 100 patients, the first 250 patients, and quarterly for the remaining 750 patients.

43. ***11.2 Trial Monitoring***

Old Text: The groups charged with monitoring the various aspects of the study will be: the VERVE Steering Committee, the Data Safety Monitoring Board, UAB IRB (for the Coordinating Center) and the UAB Coordinating Center.

New Text: The groups charged with monitoring the various aspects of the study will be: the VERVE Steering Committee, the Data Safety Monitoring Board (expected to be appointed by the NIH, conditional on NIH funding), UAB IRB (for the Coordinating Center) and the UAB Coordinating Center.

44. *11.3 Data Handling*

Old Text: Each site will be provided with access to the data entry application (RedCap ®) in order to optimize the management of the large number of subjects and to allow timely submission of data to a central database at the Coordinating Center. A security system will be maintained that prevents unauthorized access to data and each site staff will have a unique sign on code. Visit data will be captured through the RedCap ® and the Coordinating Center staff will have direct access to this data to review and monitor on a frequent basis.

New Text: Each site will be provided with access to the data entry application (Velos ®) in order to optimize the management of the large number of subjects and to allow timely submission of data to a central database at the Coordinating Center. A security system will be maintained that prevents unauthorized access to data and each site staff will have a unique sign on code. Visit data will be captured through the Velos ® and the Coordinating Center staff will have direct access to this data to review and monitor on a frequent basis.

45. *13.1 Shipment of Specimens, page 44*

Old Text: The green top tubes for the processing of PBMCs will be shipped overnight to Dr. Messaoudi's laboratory at VGTI, and the purple top tubes will be shipped overnight to the UAB Biorepository for isolation of DNA, buffy coat and plasma. All serum specimens will be shipped in batches to the UAB Biorepository on dry ice. Shipments will occur on all days of the week except Saturday or Sunday by express courier. The Coordinating Center will be informed electronically of the shipment (return receipt). Once received, all specimens will be bar coded and separated from those for PCR determinations versus those for the biorepository.

New Text: The green top tubes for PBMCs, the purple top tubes for isolation of DNA, buffy coat and plasma and serum separate specimens in combo-boxes will be shipped overnight to the UAB Biorepository. Shipments will occur on all days of the week except Saturday or Sunday by express courier. The Coordinating Center and Biorepository will be informed electronically of the shipment (return receipt). Once received, all specimens will be bar coded and separated from those for PCR determinations versus those for the Biorepository.

Amendment Version 4

1. ***3.4.4 Schedule of Study Visits***

   Old Text: a 2 week window after 6 weeks is permissible (i.e. visit may occur 6-8 weeks after randomization)

   New Text: Visit window for 6 week visit includes: -2 days or +14 days (i.e. visit may occur 40 days after randomization or 6-8 weeks after randomization)

2. ***3.4.1 Inclusion Criteria***

   Old Text: Must be currently treated with an anti-TNF therapy at the time of vaccination. Specifically, most recent weekly etanercept dose must have occurred within 7 days, most recent adalimumab dose must have occurred within 14 days, most recent certolizumab dose must have occurred within 14 days, most recent golimumab dose must have occurred within 30 days, and most recent infliximab infusion must have occurred within 56 days.

   New Text: Must be currently treated with an anti-TNF therapy at the time of vaccination. Specifically, most recent weekly etanercept dose must have occurred within 7-9 days, most recent adalimumab dose must have occurred within 14-16 days, most recent certolizumab dose must have occurred within 14-16 days, most recent golimumab dose must have occurred within 23-30 days, and most recent infliximab infusion must have occurred within 49-56 days.

3. ***3.4.4 Schedule of Study Visits***

   Old Text: Phase I: day 3 weekly until week 6 Phase I and II: 6 months

   New Text: Phase I: Day 3 (+2), weekly until week 6 Phase I and II: 6 months

4. ***3.1 Study Overview***

   Old Text: Participants will be contacted by telephone three (3) days after receiving either Zostavax® or Placebo

   New Text: Participants will be contacted by telephone three- five (3-5) days after receiving either Zostavax® or Placebo

5. ***3.4.4 Schedule of Study Visits***
   Old Diagram:

Activity per Protocol	Phase I Office-Based n=250 patients			Phase II Office-Based n=750 patients		Phase I & II Follow Up Visits			
Visits	#0 Screen*	#1 Baseline	#2 F/U	#1 Baseline	#2 F/U	F/U Phone Call Safety	Extended F/U 500 VO†	F/U via Claims Data	Unsch
Visit Time (Weeks/Years)		Wk 0	Wk 6***	Wk 0	Wk 6***	Phase I: day 3 weekly until week 6 Phase I and II: 6 months	Year 1 & annually for 10 years**	long-term**	As Needed
Informed Consent	X			X					
Inclusion/Exclusion Criteria (Eligibility)	X			X					
Vital Signs		X	X	X	X				X
Baseline Demographics		X		X					
Screening Questionnaire		X		X					
CDAI		X	X	X	X				
RAPID3		X	X	X	X				
ELISPOT (For VZV IgG, 1 SST)	X								
Zostavax Vaccine/Placebo		X		X					
Immunogenicity (PBMC, gp-Elisa) 2 green top at screening (250 in Phase I; 750 in Phase II; all 500 vaccinated pts, annually		X (250)	X (250)	X (750)	X (750)		X (500)		
UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma		X	X	X	X				
Randomization & Study Medication Administration unblinded		X		X					
Post vaccination Rash-Doctors Office as Needed									X
Safety Telephone Call						X (1000)			
Records request to confirm HZ and/or PHN			X		X	X			X
Annual clinical assessment & blood draw for patients that were given Zoster Vaccine							X		
Outcomes assessment via claims data with possible medical record confirmation								X	
Photograph/Swab for PCR lesions & scabs as needed to UAB									X
Concomitant Medication		X	X	X	X	X			X
Adverse Events		X	X	X	X	X			X

New Diagram:

Activity per Protocol	Phase I Office-Based n=250 patients	Phase II Office-Based n=750 patients	Phase I & II Follow Up Visits

Visits	#0 Screen*	#1 Baseline	#2 F/U	#1 Baseline	#2 F/U	F/U Phone Call Safety	Extended F/U 500 VO†	F/U via Claims Data	Unsch
Visit Time (Weeks/Years)		Wk 0	Wk 6***	Wk 0	Wk 6***	Phase I: Day 3 (+2), weekly until week 6 Phase I and II: 6 months	Year 1 & annually for 10 years**	long-term**	As Needed
Informed Consent	X			X					
Inclusion/Exclusion Criteria (Eligibility)		X		X					
Vital Signs		X	X	X	X				X
Baseline Demographics		X		X					
Screening Questionnaire		X		X					
CDAI		X	X	X	X				
RAPID3		X	X	X	X				
ELISPOT (For VZV IgG, 1 SST)	X								
Zostavax Vaccine/Placebo		X		X					
Immunogenicity (PBMC, gp-Elisa) 2 green top at screening (250 in Phase I; 750 in Phase II; all 500 vaccinated pts, annually		X (250)	X (250)	X (750)	X (750)		X (500)		
UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma		X	X	X	X				
Randomization & Study Medication Administration unblinded		X		X					
Post vaccination Rash-Doctors Office as Needed									X
Safety Telephone Call						X (1000)			
Records request to confirm HZ and/or PHN			X		X	X			X
Annual clinical assessment & blood draw for patients that were given Zoster Vaccine							X		
Outcomes assessment via claims data with possible medical record confirmation								X	
Photograph/Swab for PCR lesions & scabs as needed to UAB									X
Concomitant Medication		X	X	X	X	X			X
Adverse Events		X	X	X	X	X			X

Amendment Version 5

1. *3.2 Data Collection for Phase I*

Old Text: Initially, Phase Ia will recruit 50 patients at the University Alabama Birmingham (UAB) and 50 patients at Oregon Health and Science University (OHSU) rheumatology clinics who are being treated with anti-TNF therapy with or without DMARDs, and who test positive for Varicella IgG. They will also receive once weekly phone calls from study site nurses at UAB and OHSU to prompt for information regarding AEs and SAEs of interest.
Varicella IgG status must be known at or prior to randomization and may be used as long as it is verified as positive within one year prior to randomization.

New Text: Initially, Phase Ia will recruit the first 100 patients who are being treated with an anti-TNF therapy with or without DMARDs, and who test positive for Varicella IgG from the University of Alabama at Birmingham (UAB), Oregon Health and Science University (OHSU) rheumatology clinics, and other select clinical sites if needed. They will also receive once weekly phone calls from study site staff to prompt for information regarding AEs and SAEs of interest.
Varicella IgG status must be known at or prior to randomization and may be used as long as it is verified as positive within three years prior to randomization.

2. ***3.2 Data Collection for Phase I***
   Old Text: 3.2 Data Collection for Phase I
   New Text: 3.2 Data Collection for Phase I and Phase II

3. ***3.3 Phase II***
   Old Text: 3.3 Phase II
   New Text: 3.3 Storage of Specimens for Future Use

4. ***3.3 Storage of Specimens for Future Use***
   Old Text: Phase II moved to section 3.2
   New Text: As part of this study, blood specimens collected from participants will be stored for future research on arthritis, other auto-immune related diseases, inflammation, and varicella. The purpose is to make the specimens available for future research that is not yet planned. The future research may be conducted by Jeffrey Curtis, MD from the University of Alabama at Birmingham or by other researchers that obtain Institutional Review Board (IRB) approval for their research. Specimens will be stored in a central location at the UAB VERVE Coordinating Center Biorepository. Storing specimens is not an optional part with respect to participation within the study. However, participants have the option to choose whether or not they would like their specimens to be used for possible future research. Participants will indicate on the informed consent document whether or not they agree to allow specimens to be kept and used for future research involving other diseases.

   The specimens stored will be labeled with a unique de-identified study subject number. Researchers are required to protect participant's privacy and keep information private to the extent permitted by law. Clinical data associated with the specimens will be entered

to the online electronic data capture system, Velos, used for the trial. All data captured will be secured and locked on a password protected computer database.

The results of tests performed on stored samples for future research will not be given to participants. There will be no benefit for participants from the storage of specimens. However, the specimens obtained from participants in this research may help in the development of a future commercial product. There are no plans to provide financial compensation if this occurs.

Participants can request by written letter to withdraw from the study and have their unused research specimens destroyed. Participants will submit their request in writing to the UAB VERVE Study, Attn: Dr. Jeffrey R Curtis via fax: (205) 934-1301 or mail: 1720 2nd Avenue South, AB 470, Birmingham, AL 35294-0104. If participants do not submit a written request to withdraw from the study, specimens will be stored indefinitely or until used.

5. ***3.4.1 Inclusion Criteria***

   Old Text: Must be currently treated with an anti-TNF therapy at the time of vaccination. Specifically, most recent weekly etanercept dose must have occurred within 7-9 days, most recent adalimumab dose must have occurred within 14-16 days, most recent certolizumab dose must have occurred within 14-16 days, most recent golimumab dose must have occurred within 23-30 days, and most recent infliximab infusion must have occurred within 49-56 days.

   New Text: Must be currently treated with an anti-TNF therapy at the time of study drug administration. Specifically, meets one of the following:
   Etanercept dose within 9 days (1 week + 2 days)
   Adalimumab dose within 16 days (2 weeks + 2 days)
   Certolizumab SC (q2 weeks) dose within 16 days (2 weeks + 2 days)
   Certolizumab SC (q4 weeks) dose within 16 days (2 weeks + 2 days)
   Golimumab SC (q4 weeks) dose within 32 days (4 weeks + 4 days)
   Golimumab IV (q8 weeks) dose within 64 days (9 weeks + 1 day)
   Infliximab IV (q8 weeks) dose within last 64 days (9 weeks + 1 day)
   (Date of previous dose of medication is required)

6. ***3.4.2 Exclusion Criteria***

   New Text: Documented VZV negative result

7. ***3.4.8 Blinding***

   Old Text: Therefore, each site will have an un-blinded nurse who is able to give the vaccine or placebo (saline) injection in an opaque syringe. The un-blinded nurse is required to be independent of the study and is not a member of the sponsoring organization.

New Text: Therefore, each site will have un-blinded site medication administration personnel delegated by the Investigator who is able to give the vaccine or placebo (saline) injection in a blinded fashion, with patients wearing an eye mask. The un-blinded medication administration personnel will have no other involvement in the study.

8. ***13 Specimen Collection***
   Old Text: It will be coded with the patient's identification number and frozen at -85 degrees C until shipped to the biorepository at the Coordinating Center.

   Regarding blood collection, serum will be separated from whole blood following low-speed standard centrifugation, transferred to plastic cryovials and coded with the patient's identification number. The blood will be stored at -85 degrees C until shipped with other specimens to the biorepository.

   New Text: It will be coded with the patient's identification number and frozen at -20 up to -80 degrees C until shipped to the UAB VERVE Coordinating Center Biorepository

   Regarding blood collection, serum will be separated from whole blood following low-speed standard centrifugation, transferred to plastic cryovials and coded with the patient's identification number. The blood will be stored at -20 up to -80 degrees C until shipped with other specimens to the biorepository.

Amendment Version 6

1. ***1.1 Herpes Zoster and Zoster Vaccine***
   Old Text: In the SPS, a pivotal study of 38,456 adults aged ≥ 60 years led by Dr. Michael Oxman, the vaccine reduced the burden of illness (BOI) and the incidence of HZ and PHN 66.5%.

   New Text: In the **Shingles Prevention Study (SPS),** a pivotal study of 38,456 adults aged ≥ 60 years led by Dr. Michael Oxman, the vaccine reduced the burden of illness (BOI) and the incidence of HZ and PHN 66.5%.

2. ***3.1 Study Overview***
   Old Text: The VaricElla zosteR VaccinE (VERVE) trial is a 2-arm, double-blinded, multicenter randomized pragmatic clinical trial designed to determine whether the currently licensed zoster vaccine is safe and effective in patients with inflammatory arthritis using anti-TNF therapies. We propose to recruit 1,000 patients 50 years or older currently using any anti-TNF therapy from rheumatology practices and randomize these participants (1:1) to receive either the HZ vaccine or placebo (saline).Study procedures will be facilitated on site after site has received Institutional Review Board approval for this study.

New Text: The VaricElla zosteR VaccinE (VERVE) trial is a 2-arm, double-blinded, multicenter randomized pragmatic clinical trial designed to determine whether the currently licensed zoster vaccine is safe and effective in patients with inflammatory arthritis **and other diseases requiring use of** anti-TNF therapies. We propose to recruit 1,000 patients 50 years or older currently using any anti-TNF therapy from **clinical** practices and randomize these participants (1:1) to receive either the HZ vaccine or placebo (saline).Study procedures will be facilitated on site after site has received Institutional Review Board approval for this study.

Rationale: Changes per recent FDA and DSMB feedback; purpose is to maximize generalizability of the trial.

3. ***3.1 Study Overview***

Old Text: For all participants who are enrolled in a health plan with data that can be linked to VERVE (e.g. Medicare), effectiveness follow-up will be assessed after randomization and will rely on linked administrative data (medical, pharmacy claims). Patients will be consented for this linkage and sign a HIPAA authorization to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information, including linkage with health plan data.

New Text: For all participants who are enrolled in a health plan with data that can be linked to VERVE (e.g. Medicare), effectiveness follow-up will be assessed after randomization and will rely on linked administrative data (medical, pharmacy claims). Patients will be consented for this linkage and **required to sign a VERVE study specific authorization form** to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information, including linkage with health plan data. **In addition to the VERVE study specific authorization form, sites may have a site specific form, if required by a local institutional review board, but it will not replace the required VERVE form. The VERVE study specific authorization form has been reviewed and approved for use by the University of Alabama at Birmingham Institutional Review Board under the VERVE Coordinating Center protocol.**

Rationale: Changes made due to recent feedback from local IRBs

4. ***3.2 Data Collection for Phase I and Phase II***

Old Text: Initially, Phase Ia will recruit the first 100 patients who are being treated with an anti-TNF therapy with or without DMARDs, and who test positive for Varicella IgG from the University of Alabama at Birmingham (UAB), Oregon Health and Science University (OHSU) rheumatology clinics, and other select clinical sites if needed. Varicella IgG status must be known at or prior to randomization and may be used as long as it is verified as positive within three years prior to randomization. For these first 100 patients, and consistent with the FDA guidance provided during our pre-IND meetings with FDA, any patients having received any parenteral or oral corticosteroids in the last 30 days will be excluded.

New Text: **Phase Ia and Phase Ib**
Initially, Phase Ia will recruit **patients** who are being treated with an anti-TNF therapy with or without DMARDs, and who test positive for Varicella IgG from the University of Alabama at Birmingham (UAB), Oregon Health and Science University (OHSU) rheumatology clinics, and other select clinical sites if needed. Varicella IgG status must be known at or prior to randomization and may be used as long as it is verified as positive within three years prior to randomization. **For Phase Ia patients** and consistent with the FDA guidance provided during our pre-IND meetings with FDA, any patients having received any parenteral or oral corticosteroids in the last 30 days will be excluded.

Rationale: Specific numbers removed based on guidance from the DSMB and the FDA; the trial may be advanced to a subsequent phase earlier, conditional on approval from the DSMB, FDA and IRB.

5. ***3.2 Data Collection for Phase I and Phase II***
Old Text: Assuming that no serious safety concerns are identified, Phase I will continue and recruit an additional 150 patients between UAB, OHSU and at select clinical sites if needed (Phase 1b of the trial). For these 150 additional patients, confirmation of varicella IgG status must be known, as described above. However, the prohibition against use of recent or current glucocorticoid therapy will be dropped, and patients may be included if they have received prednisone-equivalent doses of up to 10 mg per day, as long as the dose has been stable for the last 30 days.

New Text: Assuming that no serious safety concerns are identified **and conditional on FDA, DSMB, and IRB approval, Phase I will continue to Phase Ib and recruit patients between UAB, OHSU and select clinical sites. For these additional patients**, confirmation of varicella IgG status must be known, as described above. However, the prohibition against use of recent or current glucocorticoid therapy will be dropped, and patients may be included if they have received prednisone-equivalent doses of up to 10 mg per day, as long as the dose has been stable for the last 30 days. **The initial expectation is that Phase 1a will enroll approximately 100 patients, and phase 1b will enroll approximately 150 additional patients to yield a total of 250 patients in Phase 1 overall. However, these specific numbers are conditional on guidance from the DSMB and the FDA; and the trial may be advanced to a subsequent phase earlier conditional on approval from the DSMB, FDA and IRB.**

Rationale: Specific numbers removed based on guidance from the DSMB and the FDA; the trial may be advanced to a subsequent phase earlier, conditional on approval from the DSMB, FDA and IRB.

6. ***3.2 Data Collection for Phase I and Phase II***
Old Text: **Phase II**

The second phase of the trial will enroll 750 patients from additional academic and community sites. The eligibility criteria are the same with those from the end of the Phase I study, but with the removal of the positive VZV test criteria. Safety data that will support the primary outcome of the trial will be collected via a scheduled in-clinic visit 6 weeks after vaccination and a 6 month phone call. Patients will also be instructed to report any AEs suggestive of a VZV event and any SAEs that occur within the first 42 days promptly to their study physician and return for an in-person visit as soon as they may occur.

New Text: **Phase II**
The second phase of the trial **(Phase II) will enroll to a total of 1000 patients** from additional academic and community sites. The eligibility criteria are the same with those from the end of the Phase I study, but with the removal of the positive VZV test criteria. Safety data that will support the primary outcome of the trial will be collected via a scheduled in-clinic visit 6 weeks after vaccination and a 6 month phone call. Patients will also be instructed to report any AEs suggestive of a VZV event and any SAEs that occur within the first 42 days promptly to their study physician and return for an in-person visit as soon as they may occur.

Rationale: Specific numbers removed based on guidance from the DSMB and the FDA; the trial may be advanced to a subsequent phase earlier, conditional on approval from the DSMB, FDA and IRB.

7. ***3.4.1 Inclusion Criteria***

Old Text: Must be currently treated with an anti-TNF therapy at the time of study drug administration. Specifically, meets one of the following:

New Text: Must be currently treated with an anti-TNF therapy at the time of study drug administration, **allowing for small deviations in dosing frequency and logistic feasibility (e.g. study visits to occur on a week day)**. Specifically, meets one of the following:

8. ***3.4.1 Inclusion Criteria***
Old Text: Certolizumab SC (q2 weeks) dose within 16 days (2 weeks + 2 days)
Certolizumab SC (q4 weeks) dose within 16 days (2 weeks + 2 days)

New Text: Certolizumab SC (q2 weeks) dose within 16 days (2 weeks + 2 days)
Certolizumab SC (q4 weeks) dose within 32 days (4 weeks + 4 days)

Rationale: Revised text corrects previous error in dosing window

9. ***3.4.1 Inclusion Criteria***
Old Text: Diagnosis of RA or another inflammatory arthritis

New Text: Diagnosis of RA or another inflammatory arthritis **(Phase Ia); or RA, another inflammatory arthritis, or other inflammatory condition (e.g. psoriasis) requiring use of anti-TNF therapy (Phase Ib and II)**

Rationale: Changes per recent FDA and DSMB feedback; purpose is to maximize generalizability of the trial.

10. ***3.4.1 Inclusion Criteria***

Old Text: The first 250 patients recruited to Phase I must test positive for VZV IgG.

New Text: **Phase I subjects** must test positive for VZV IgG

Rationale: Specific numbers removed based on guidance from the DSMB and the FDA; the trial may be advanced to a subsequent phase earlier, conditional on approval from the DSMB, FDA and IRB.

11. ***3.4.1 Inclusion Criteria***

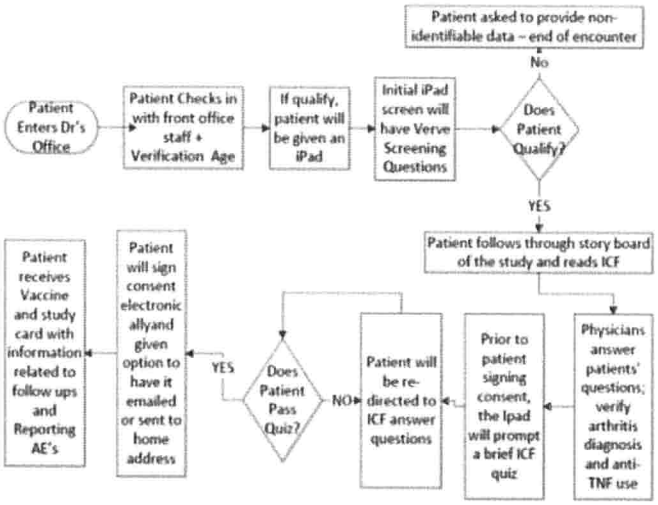
Old Text: The first 100 patients recruited to phase I must not have received any oral or systemic glucocorticoids within 30 days prior to vaccination. Intra-articular glucocorticoid injections within the previous 30 days are acceptable.

New Text: **Phase Ia subjects** must not have received any oral or systemic glucocorticoids within 30 days prior to vaccination. Intra-articular glucocorticoid injections **and inhaled glucocorticoids** within the previous 30 days are acceptable.

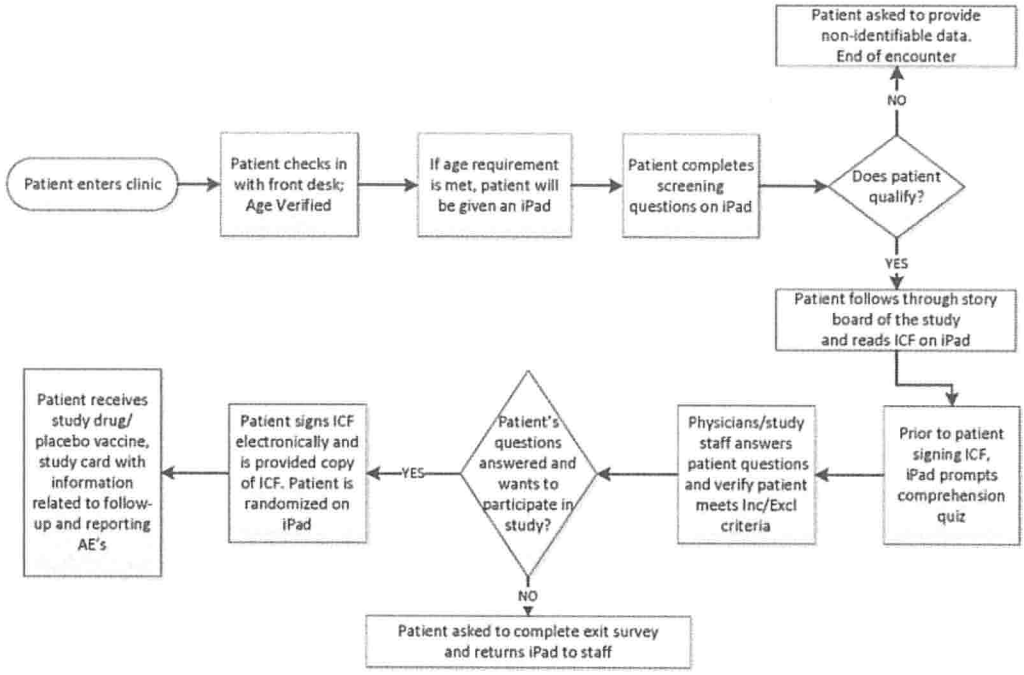
Rationale: Specific numbers removed based on guidance from the DSMB and the FDA; text added from recent site inquiry about specific glucocorticoids.

12. ***3.4.3 Study Conduct, Figure 1***

Old Text:



New Text:



13. ***3.4.4 Schedule of Study Visits***

Old Text:

Title Row: Phase I Office-Based n=250 patients; Phase II Office-Based n=750 patients

Row: Immunogenicity (PBMC, gp-Elisa) 2 green top at screening (250 in Phase I; 750 in Phase II; all 500 vaccinated pts, annually

Row: UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma

***Note**: Phase I refers to the first 250 patients; Phase II refers to the remaining 750 patients

Activity per Protocol	Phase I Office-Based N=250 patients	Phase II Office-Based N=750 patients	Phase I & II Follow Up Visits

Immunogenicity (PBMC, gp-Elisa) 2 green top at screening (250 in Phase I; 750 in Phase II; all 500 vaccinated pts, annually		X (250)	X (250)	X (750)	X (750)		X (500)		

UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma		X	X	X	X				

New Text:

n=250, n=750 removed from title headers

Activity per Protocol	Phase I Office-Based	Phase II Office-Based	Phase I & II Follow Up Visits

Immunogenicity (PBMC, gp-Elisa) **3** green top at screening; numbers under X removed

Immunogenicity (PBMC, gp-Elisa) **3** green top at screening		X	X	X	X		X		

X added in column under phase I & II follow up visits

UAB Biorepository Collect 1 purple, 1 SST to archive serum, DNA, buffy coat and plasma		X	X	X	X		**X**		

*Note removed from table

14. ***3.4.6 Informed Consent***

Old Text: Health care providers and office staff at the participating rheumatology practices will receive web-based training in the informed consent process. Eligible patients will be consented by study staff before any study related activities are initiated. Patients will have the opportunity to ask the study physician any questions and can proceed to sign the consent. As part of this process, participants will be asked to provide consent to link study-related data to administrative data (e.g. Medicare) and to sign a generic release of information and a HIPAA authorization for future procurement of medical records related to study outcomes in the event these are needed.

New Text: Health care providers and office staff at the **participating practices** will receive web-based training in the informed consent process. Eligible patients will be consented by study staff before any study related activities are initiated. Patients will have the opportunity to ask the study physician any questions and can proceed to sign the consent. As part of this process, participants will be asked to provide consent to link

study-related data to administrative data (e.g. Medicare) and **are required to sign a VERVE study specific authorization form to allow follow-up contact (within the first 6 weeks, or beyond) to obtain medical records or other additional information** related to study outcomes in the event these are needed.

Rationale: Text removed for generalizability for participating practices; text added to this section to remain consistent in verbiage throughout protocol.

15. ***4 Adverse Events***

Old Text: 4 Adverse Events

New Text: 4 Adverse Events and Potential Risks

New Text: Potential Risks with the Zoster Vaccine

The following problems may be caused by the study injection. If they occur, they are expected within the first 4-6 weeks from the time of injection.

- Injection under the skin of the upper arm may cause some local discomfort including such symptoms as swelling, redness, warmth, tenderness or slight bruising. This is the most common side effect of the vaccine.
- Other possible risks include the following:
    - Eye pain or visual changes
    - A rash at the site of the injection or elsewhere that can look like 'chickenpox'
    - Coughing
    - Stiff neck
    - Fever
    - A 'welt' or 'hives' at the site of injection
    - Flare of your arthritis
    - Nausea
    - Headache
    - Allergic reactions, which may be serious and may include difficulty in breathing or swallowing. If an allergic reaction occurs, subjects are to notify doctor right away, call 911, and go to the nearest ER
    - Swollen glands near the injection site that may last a few days to few weeks
    - Pain such as burning, aching, tingling, or sensitivity of one area of the body

Rationale: List of potential risks added to protocol as this list is mentioned in the informed consent document in this format; recent feedback from participating sites and local IRBs.

16. ***4.3.2 Procedures for Reporting and Recording***

Old Text: For the very small number of cases needing clinical adjudication (non-cutaneous cases and cutaneous-cases lacking adequate laboratory specimens), it will be unknown if they are due to vaccine-strain virus. Thus, they will be able to meet the case definition for suspected vaccine-strain VZV, but not PCR-confirmed vaccine-strain VZV. Therefore, these cases will be included in the outcome events analyzed for the primary outcome, assuming they are adjudicated as probable or confirmed following clinical adjudication Clinically adjudicated cases will be excluded as part of a sensitivity

analysis that will be reported as a secondary endpoint of the trial of PCR-confirmed vaccine-strain VZV events.

New Text: For the very small number of cases needing clinical adjudication (non-cutaneous cases and cutaneous-cases lacking adequate laboratory specimens), it will be unknown if they are due to vaccine-strain virus. Thus, they will be able to meet the case definition for suspected vaccine-strain VZV, but not PCR-confirmed vaccine-strain VZV. Therefore, these cases will be included in the outcome events analyzed for the primary outcome, assuming they are adjudicated as probable or confirmed following clinical adjudication **based upon clinical data, including digital images (if available). A clinician with expertise in identifying varicella infection will be appointed as a safety monitor and will be responsible for initial triage and clinical adjudication, with additional input from the DSMB as indicated.** Clinically adjudicated cases will be excluded as part of a sensitivity analysis that will be reported as a secondary endpoint of the trial of PCR-confirmed vaccine-strain VZV events.

Rationale: Text added to create the role of a safety monitor to triage and preliminary adjudicate clinical cases to safeguard against conflict.

17. ***5.1 Definition***

Old Text: Tolerability of vaccination using patient diaries (Phase I, first 250 patients, using data collected at 6 week in-person visit)

New Text: Tolerability of vaccination using patient diaries (**Phase I** using data collected at 6 week in-person visit)

Rationale: Specific numbers removed based on guidance from the DSMB and the FDA

18. ***6.5.1 Stopping Rules for Confirmed Vaccine-Strain VZV Cases***

New Text: Enrollment between phases of the trial will be continuous, meaning that after each of the phase 1a and phase 1b recruitment targets have been met, the DSMB and FDA will be provided the data to consider advancing the study to the next phase. During this period of time (expected to be relatively short [e.g. 1-2 months]), enrollment may continue under the prior inclusion criteria and need not be halted.

Rationale: Enrollment/recruitment remains continuous and unbroken as data is reviewed.

19. ***8 DSMB Governance***

Old Text: The DSMB will receive data periodically (e.g. quarterly) including pre-specified time points including after the first 100 patients, the first 250 patients, and quarterly for the remaining 750 patients.

The pre-specified stopping rules outlined in section 6.3 will be adhered to…

New Text: The DSMB will receive data periodically (e.g. quarterly) including pre-specified time points including after the first 100 patients, the first 250 patients, and quarterly for the remaining 750 patients. **Enrollment will not need to be halted during periods of DSMB consideration, but explicit DSMB and FDA approval is required to advance the inclusion criteria to the next phase of the study (Ia to Ib, and Ib to II).**

The pre-specified stopping rules outlined in **section 6.5** will be adhered to…
Rationale: Enrollment/recruitment remains continuous during periods of review. FDA, DSMB designate when to move to next phase of trial.

Amendment Version 7

1. ***2.1 Primary Objectives and endpoint***

   New Text: Patients who have a 6 week visit (with labs) have sufficient data to be considered complete for the primary lab-based outcome.

2. ***3.1 Study Design***

   New Text: The main study is 6 months in duration. Everything beyond the 6 month telephone contact is considered the extension phase of the study and is relevant only for intervention patients and not placebo-treated patients.

3. ***3.4.1 Inclusion Criteria***

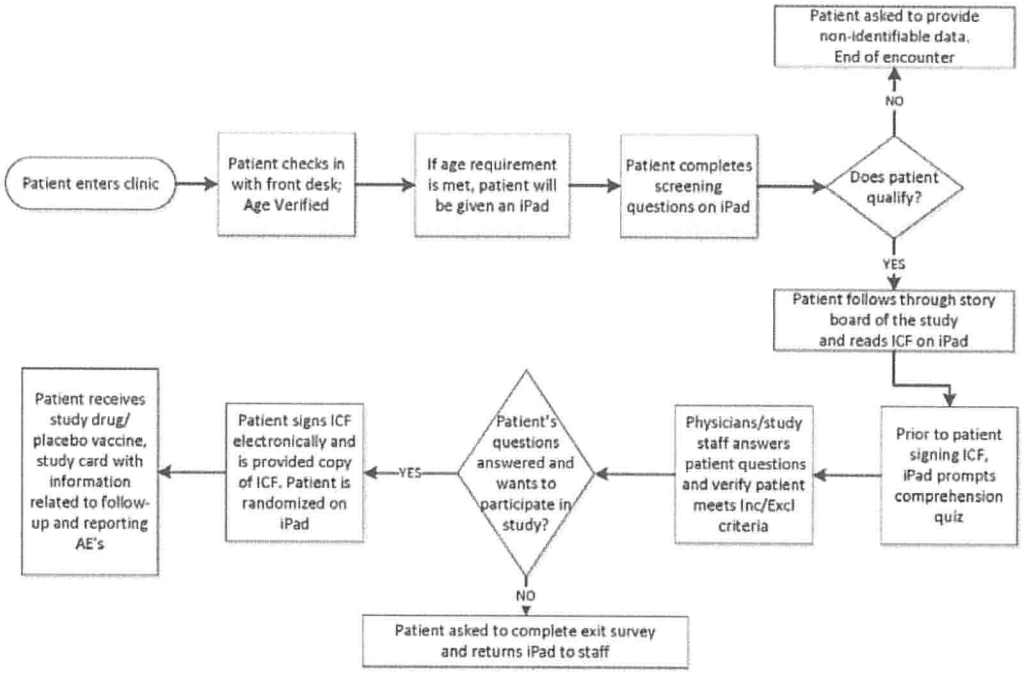
   Old Text: Must be currently treated with an anti-TNF therapy at the time of study drug administration, allowing for small deviations in dosing frequency and logistic feasibility (e.g. study visits to occur on a week day). Specifically, meets one of the following:
   Etanercept dose within 9 days (1 week + 2 days)
   Adalimumab dose within 16 days (2 weeks + 2 days)
   Certolizumab SC (q2 weeks) dose within 16 days (2 weeks + 2 days)
   Certolizumab SC (q4 weeks) dose within 32 days (4 weeks + 4 days)
   Golimumab SC (q4 weeks) dose within 32 days (4 weeks + 4 days)
   Golimumab IV (q8 weeks) dose within 64 days (9 weeks + 1 day)
   Infliximab IV (q8 weeks) dose within last 64 days (9 weeks + 1 day)
   (Date of previous dose of medication is required)

   New Text: Must be currently treated with an anti-TNF therapy** at the time of study drug administration, allowing for small deviations in dosing frequency and logistic feasibility (e.g. study visits to occur on a week day). **Date of previous dose of medication is required.** Specifically, meets one of the following:
   Etanercept dose within 9 days (1 week + 2 days)
   Adalimumab dose within 16 days (2 weeks + 2 days)
   Certolizumab SC dose within 16 to 32 days depending on dosing frequency schedule (2 weeks + 2 days, or 4 weeks + 4 days)
   Golimumab SC dose within 32 days (4 weeks + 4 days)

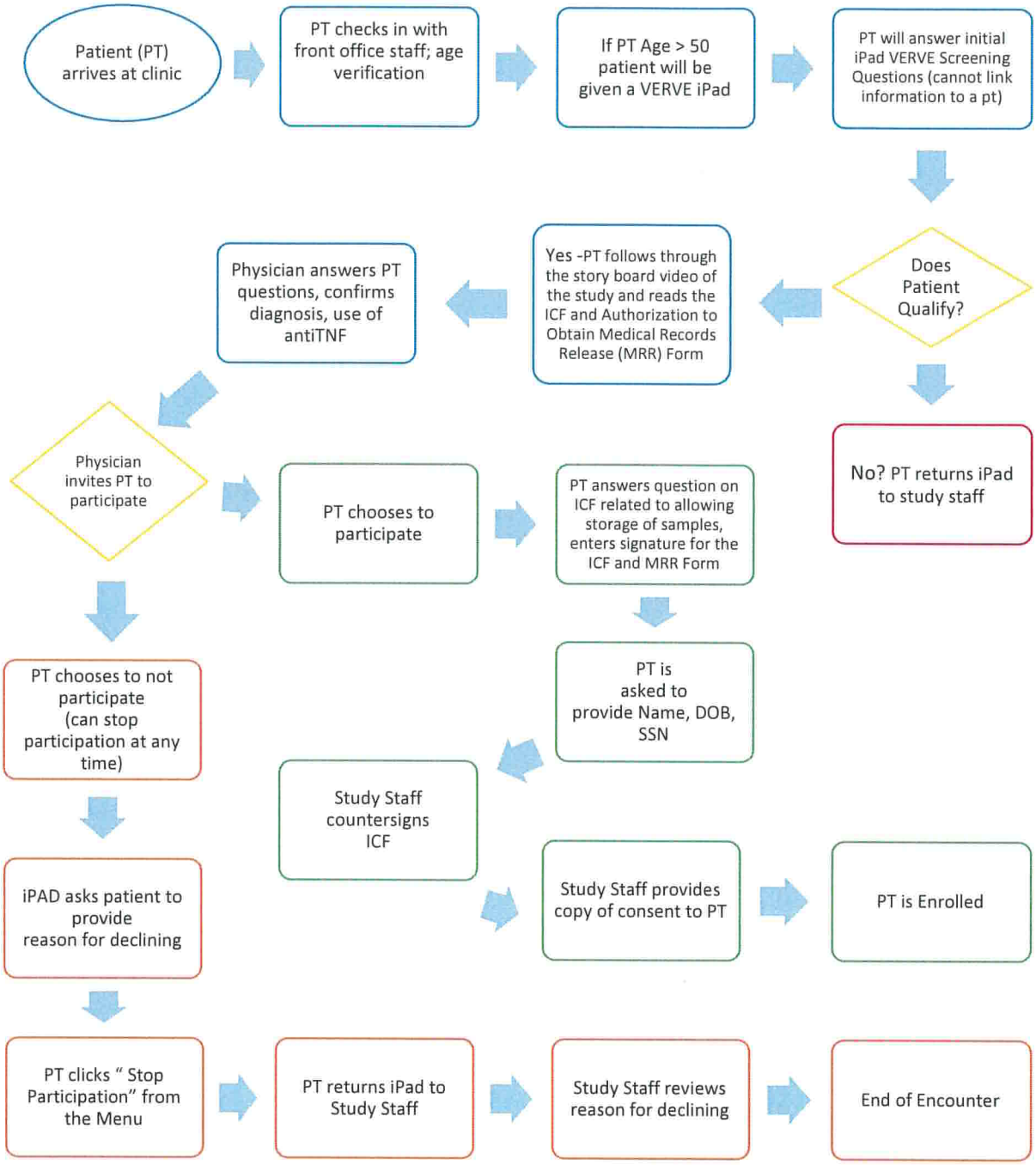
Golimumab IV dose within 64 days (9 weeks + 1 day)
Infliximab IV dose within last 64 days (9 weeks + 1 day)
**** any form of biosimilar for the above listed anti-TNF medications is acceptable**

4. 3.4.3 Study Conduct

Old Text:



New Text:


Patient (PT) arrives at clinic
PT checks in with front office staff; age verification
If PT Age > 50 patient will be given a VERVE iPad
PT will answer initial iPad VERVE Screening Questions (cannot link information to a pt)
Does Patient Qualify?
No? PT returns iPad to study staff
Yes -PT follows through the story board video of the study and reads the ICF and Authorization to Obtain Medical Records Release (MRR) Form
Physician answers PT questions, confirms diagnosis, use of antiTNF
Physician invites PT to participate
PT chooses to participate
PT answers question on ICF related to allowing storage of samples, enters signature for the ICF and MRR Form
PT is asked to provide Name, DOB, SSN
Study Staff countersigns ICF
Study Staff provides copy of consent to PT
PT is Enrolled
PT chooses to not participate (can stop participation at any time)
iPAD asks patient to provide reason for declining
PT clicks " Stop Participation" from the Menu
PT returns iPad to Study Staff
Study Staff reviews reason for declining
End of Encounter

5. *3.4.4 Schedule of Events*

Old Text:

Visit Time (Weeks/Years)		Wk 0	Wk 6***	Wk 0	Wk 6***	Phase I: Day 3 (+2), weekly until week 6 Phase I and II: 6 months	Year 1 & annually for 10 years**	long-term**	As Needed
Randomization & Study Medication Administration un-blinded		X		X					
Annual clinical assessment & blood draw for patients that were given Zoster Vaccine							X		

New Text:

Visit Time (Weeks/Years)		Wk 0	Wk 6***	Wk 0	Wk 6***	**Day 3 (+2), Week 1-5, Week 6, 6 months**	Year 1 & annually for 10 years**	long-term**	As Needed
Randomization & Study Medication Administration **by un-blinded staff**		X		X					
Annual clinical assessment & blood draw for patients that were given Zoster Vaccine							X **(500)**		

6. ***4 Adverse Events and Potential Risks***

Old Text: Related: There is a reasonable causal relationship between study drug administration and the AE.
Not related: There is not a reasonable causal relationship between study drug administration and the AE.

New Text: Related (**Related, Likely, Possibly, or Probably Related**): There is a reasonable causal relationship between study drug administration and the AE.
Not related (**Not Related, Unrelated, Unlikely**): There is not a reasonable causal relationship between study drug administration and the AE.
Unknown: The relationship between study drug administration and the AE cannot be determined.

7. ***4.1.1 Serious Adverse Event Collection and Reporting***

Old Text: Following the subject's written consent to participate in the study and randomization, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur after the medication administration and within 6 months of dosing.

New Text: Following the subject's written consent to participate in the study and randomization, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. **Serious Adverse Events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Serious Adverse Events (SAEs) are collected from Randomization through Day 183 post randomization for all participants in both treatment arms. Because of a lack of biologic plausibility and because there is no longer a control group under active follow-up past day 183, there will be no SAEs collected past day 183. Outpatient (i.e. non-hospitalized) zoster related events are not considered as SAEs past day 183.**

Amendment Version 8

1. ***6.5.3. Interim Analysis for Sample Size Evaluation***

New Text: Due to the FDA approval of Shingrix and the expected impact on enrollment into the VERVE trial, it may be necessary to perform an interim analysis to determine if the data that has been collected in VERVE aligns with the estimated values utilized for power and sample size estimation during study planning. VERVE will monitor recruitment from August – October 2018 and compare it to the same time frame in 2017 immediately prior to Shingrix approval. The results will be presented to and discussed with the DSMB at its December 2018 meeting (or at the next meeting thereafter). If VERVE recruitment has slowed appreciably, the DSMB will likely request an interim analysis.

The interim analysis will be limited to estimation of the geometric mean fold change (GMFC) and standard deviation of the GMFC from baseline to week 6 in the active and placebo VERVE groups for the IgG (ELISPOT) and IFN (gp-ELISA) primary outcomes as described in section 6.4.1. As this was not a planned interim analysis, the alpha spending approach of Lan-DeMets (Stat Biosci (2009) 1: 95–111) will be used for 1 interim analysis at 50% of the data collection (N=500 / 1000) reaching the primary endpoint of 6 weeks. The interim alpha level will be set to 0.002787, with the final alpha testing family-wise error rate being maintained at alpha = 0.05. If statistical significance is not met at the interim analysis, the observed values at the interim analysis will be used to determine if the study sample size goal of 1000 can be adjusted downward to include fewer participants and still achieve statistical significance at for the primary outcomes.

Rationale: Section added per 07-09-2018 DSMB meeting recommendations

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