Immunogenicity of Herpes Zoster Subunit Vaccine in Inflammatory Bowel Disease Patients Treated With Vedolizumab

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A pilot study evaluating immunogenicity of herpes zoster subunit vaccine in inflammatory bowel disease patients treated with vedolizumab

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1.0 INTRODUCTION

1.1 Background and Scientific Rationale

Inflammatory bowel disease (IBD) is a chronic inflammatory state of the gastrointestinal tract(1) affecting 3.1 million people in the United States. (2, 3) Patients with IBD are treated with immunosuppressants that increase their risk of herpes zoster (HZ), also known as shingles. (4-6) Those with IBD have a two-fold increased risk for HZ compared to age matched controls. Because most IBD patients are treated with systemic immunosuppressants, which are an independent risk factor for HZ, the live attenuated HZ vaccine was not recommended. However, the release of the new inactivated HZ vaccine, Shingrix (GlaxoSmithKline, Brentford, UK), presents new opportunities for preventive care. The FDA recently lowered the age of Shingrix that allows all adults 18 and older to receive the vaccine.

Vedolizumab is an α4β7 integrin monoclonal antibody that mainly affects gastrointestinal mucosa and associated lymphoid tissue and may not increase the risk for HZ. It selectively downregulates gut inflammation by inhibiting intestinal T-lymphocyte trafficking, without systemic immunosuppression. (7) Vedolizumab does not appear to increase the risk for HZ.(8) A HZ subunit vaccine was recently approved and will be safe to administer to immunosuppressed IBD patients. (9) (10) Despite the known increased incidence of zoster in the IBD population, studies elucidating immunogenicity of the HZ subunit vaccine are lacking.

This proposal will evaluate the immunogenicity of the new herpes zoster subunit vaccine in IBD patients on vedolizumab compared to those on anti-tumor necrosis factor therapy in a pilot study. We will evaluate if the cell-mediated immunity to VZV is boosted with immunization. Reactivation of varicella zoster virus (VZV) results in HZ, and strong cell mediated immunity prevents reactivation of HZ. (11) (12)

Our primary goal is to evaluate the immunogenicity of the herpes zoster subunit vaccine to obtain pilot data to perform a larger immunogenicity study. We will compare the VZV-specific T cell response (cell mediate immunity) prior and after immunization with the herpes subunit vaccine in IBD patients 18-70 years old with a history of prior VZV infection and positive VZV antibody test. T cell response is critical in preventing reactivation of VZV and will be measured using an interferon gamma (IFNγ) enzyme linked immunospot (ELISPOT), the standard measure of CMI to VZV. (13) Our lab has previously evaluated T cell response to influenza and hepatitis B vaccine in lung transplant patients.(14, 15) We are currently evaluating cell-mediated immunity via ELISPOT in immunosuppressed and non-immunosuppresed IBD patients.

This pilot study will provide the preliminary data to perform a larger multi-center study evaluating the immunogenicity of the new herpes zoster vaccine in IBD patients on vedolizumab.

1.2 Study Aim and hypothesis

Determine the immunogenicity of the herpes zoster subunit vaccine in inflammatory bowel disease patients on vedolizumab compared to those on anti-TNF monotherapy. The goal of this aim is to evaluate humoral and cell mediated immunity in inflammatory bowel disease patients on vedolizumab who receive the two-dose herpes zoster vaccine. We will evaluate short term, one month after second vaccination dose and sustained immunogenicity at 6 and 12 months post vaccination.

The central hypothesis of this proposal is that IBD patients on vedolizumab should be able to mount a normal vaccine response comparable to those on anti-TNF monotherapy who might benefit from a third dose of the subunit vaccine as has been evaluated in HIV and transplant populations. (16, 17) We hypothesize that IBD patients on vedolizumab will be able to mount a superior response to those on anti-TNF therapy. A recent study showed that hepatitis B vaccine immunogenicity was not affected by vedolizumab. (18) Additionally, our preliminary data showed that IBD patients on vedolizumab were able mount a superior response to the influenza vaccine compared to those on anti-TNF therapy.

2.0 PRIMARY OBJECTIVE

The primary outcome of this study is to evaluate the immunogenicity of the herpes zoster subunit vaccine in IBD patients on vedolizumab compared to those on anti-TNF monotherapy.

Primary objective The primary objective will be the change in cell mediated immunity (CMI) as measured by ELISPOT from pre-immunization to one month after receiving second dose of vaccine. We anticipate that the change in CMI will be greater for the IBD patients on vedolizumab (Group B) compared to the IBD patients treated with anti-TNF monotherapy (Group A).

Secondary objective: **Sustained T cell response:** We will measure sustained change in CMI at 6 and 12 months post-immunization.

Secondary objective: Antibody response A secondary outcome will be the change in VZV antibody concentration from pre-immunization to one month post-immunization. This quantitative VZV antibody concentration will be in addition to the one that will be used to determine previous varicella infection for study eligibility. We will also compare the VZV antibody concentrations at 6 and 12 months following vaccine administration.

Secondary objective: vaccine adverse effects. To evaluate for adverse effects following immunization patients will receive phone calls from study personnel to ascertain vaccine-related adverse effects at months 1, 2, 3. Our study is underpowered to measure differences in adverse effects between groups. Adverse event data will be reported.

3.0 STUDY ENDPOINTS

3.1 Primary Endpoints

The primary endpoint will be evaluating the change in cell-mediated immunity (CMI) between vedolizumab and anti-TNF monotherapy patients following the two-dose herpes zoster vaccine series.

3.1 Secondary Endpoints

We will measure sustained change in CMI at 6 months' post-immunization. Another secondary endpoint will be the change in VZV antibody concentration from pre-immunization to 1 month post-immunization.

3.2 Safety Endpoints

Safety will be assessed by the incidence of adverse events (AEs) and serious adverse events (SAEs) as well as by monitoring disease activity using the Harvey-Bradshaw Index (HBI) or the Simple Colitis Activity Index (SCAI) questionnaire at the baseline visit and at three to four week post-vaccination.

4.0 STUDY DESIGN

4.1 Program Type / Scope of Study / Clinical Design / Sites

This is a single center study evaluating the immune response to herpes zoster subunit vaccine in IBD patients on vedolizumab compared to those on anti-TNF monotherapy. Patients will be recruited at the University of Wisconsin Hospital and Clinics. Humoral and cell mediated immunity will be evaluated at initial visit, and at one, 6 and 12 months after second dose of vaccine.

4.1.1 Lead Site Responsibilities

The University of Wisconsin Hospital and Clinics will be the only site for the study and be responsible for the following: coordinating activities at all sites, receiving and analyzing samples and data, and developing and updating the study protocol as needed.

Communication plan: UW will hold monthly teleconferences (lead by Freddy Caldera, UW PI) with research staff (such as research coordinator). At this teleconference, the following will be discussed: recruitment, barriers to recruitment and potential future protocol changes.

Adverse events/SAE/Unanticipated problems: All Adverse events, including adverse events to vaccines, flares of IBD and deviations from the protocol will be reported to the lead site within 3 days and reported to Takeda within 4 calendar days. The lead site will be responsible for reporting any adverse events as described in the Safety Reporting section. All fatal or life-threatening SAEs and pregnancies will be reported to the lead site and Takeda within 24 hours.

Compliance with protocol: To assure no deviations from the protocol occur, the PI will review random cases every two months. Any deviations in protocol will be further investigated to evaluate the root cause for deviation.

Changes in protocol: All changes in protocol need to be approved at University of Wisconsin.

4.2 Study Population

- Adults with established inflammatory bowel disease age 18-70
- Two study cohort will included
  - Group A IBD patients on anti-TNF monotherapy
  - Group B IBD patients on vedolizumab monotherapy

Patients in both groups should have been on stable treatment for IBD for at least three months.

4.3 Number of Subjects (Statistical Justification)

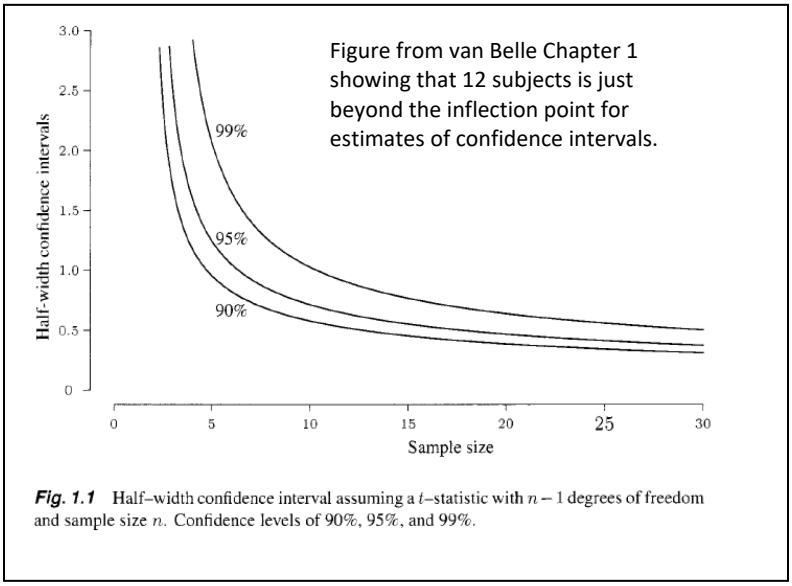


Fig. 1.1 Half–width confidence interval assuming a t–statistic with $n-1$ degrees of freedom and sample size n. Confidence levels of 90%, 95%, and 99%.

We will recruit up to total of up to 17 IBD patients on anti-TNF monotherapy (Group A) and up to 16 IBD patients on vedolizumab (Group B).

We will enroll up to 33 patients in the study. We base this sample size calculation on the Rondaan study that compared VZV immune responses measured by ELISPOT in patients with systemic lupus erythematosus (SLE) to healthy individuals (19). We used the Rondaan study's median as our estimated measure of central tendency and a conservative standard deviation estimate for the power calculation.

Group	Estimated means	Estimated standard deviation	alpha
Anti-TNF	7	8	0.05
Vedolizumab	20	12	

We will compare CMI response following subunit zoster vaccine series among IBD patients treated anti-TNF monotherapy and vedolizumab. Because there are no previous data on vaccine responses to HZ in IBD patients from which we can calculate power estimates, sample size has been determined by feasibility of recruitment at one site within a year. Our goal is to derive estimates of vaccine response results in this population to power future studies. Julious and van Belle devised the "rule of 12" as the sample size that optimizes the width of the confidence interval for pilot studies such as ours. (20) (21) The confidence interval includes the range of likely values for the population and will be useful for planning the clinical trial. (20) The width of the confidence interval decreases sharply until the sample size reaches 12 subjects in situations such as this study when we have no basis on which to estimate the variability in our sample because of lack of previous studies.

Sample size justification: We will need 12 subjects in each group for 86% power but are increasing our sample size to 15 per group to allow for 20% rate of attrition.

4.4 Statistical analysis

Descriptive statistics will be used to summarize the results. If possible, we will use nonparametric statistical tests to look for differences between the groups recognizing small sample size and pilot nature of the study design will limit our ability to draw conclusions. However, the results will allow us to plan a follow up study that will compare the efficacy of the recombinant zoster vaccine series between IBD patients treated with vedolizumab to those treated with a TNF agent.

4.5 Data Management Plan

At the University of Wisconsin, data will be stored in the UW Health electronic medical record and an excel spreadsheet on secured servers and are only accessible to those with a valid UW username and password with rights to see those files. The servers are housed in locked cabinets inside locked, climate-controlled rooms. Access to UW servers is restricted by the UW firewall. Any connections to UW servers from outside UW's network must travel over the UW Madison's virtual private network (VPN). This ensures that all communication between UW and the remote user is encrypted.

All UW servers and PC's are kept up-to-date with the latest operating system patches and anti-virus software. Network and user rights are assigned along with the principle of least privilege. Users are only given access to files they need and are restricted from all other files. All UW laptops are fully encrypted.

All final pooled data will be stored at University of Wisconsin and will only be accessible to UW research staff.

Original subject files and protocol paperwork will be kept in the secured Clinical Research Office located at the University Hospital, 600 Highland Avenue, K4/453 within locked file cabinets. Files will be stored in the research offices until 2 years after study completion at that time they will be archived and sent to the State Records Center.

Banking of specimens and data for future research:

Specimens at UW will be labeled with the subject's study ID number and date of collection so that data collected for this protocol can be linked to the sample. Samples will be stored in Rennebohm Hall at the University of Wisconsin. Only investigators and key personnel assigned to the laboratory have access to the lab. Samples will be coded (labeled with subject ID and date of collection) before they arrive to the lab. All computers used for data storage and analysis are password protected and used exclusively by key personnel.

Any future studies that will use these specimens will be done by UW researchers and will be submitted for a separate IRB approval. Only coded samples and data will be released for future research. The information linking the samples and data to individual subjects will not be released.

All data will be labeled with the subject's study ID number and stored at the University of Wisconsin. Data will be stored in an excel spreadsheet on secured servers and are only accessible to those with a valid UW username and password with rights to see those files. The servers are housed in locked cabinets inside locked, climate-controlled rooms. Access to UW servers is restricted by the UW firewall. Any connections to UW servers from outside UW's network must travel over the UW Madison's virtual private network (VPN). This ensures that all communication between UW and the remote user is encrypted.

Banked data may be used in future research to study the clinical outcomes of the Herpes Zoster vaccination, the sustained protection provided by the vaccine. The data may also be utilized to study the safety of the vaccination, and its long-term protection against Herpes Zoster.

4.6 Ethical and Regulatory Considerations

Prior to initiating study, IRB approval will be sought at University of Wisconsin School of Medicine and Public Health. Documentation of IRB approval will be sent to Takeda.

Once approval is obtained at UW. Monthly research conferences will be held by UW research staff (such as PI, research coordinator) to assure that the there are no deviations in the protocol.

Compliance with protocol: To assure no deviations from protocol occur, random cases from each site will be reviewed by the PI to assure no deviations from protocol every 2 months. Any deviations in protocol will be investigated to evaluate the route cause for deviation.

Changes in protocol: Any potential changes in protocol will first be discussed by both sites prior to implementing changes in the protocol. All changes in protocol need to be approved by University of Wisconsin. Any changes in protocol will also be sent to Takeda.

The research will be registered on clinicaltrials.gov.

We have consulted with the University of Wisconsin School of Medicine and Public Health, Institute for Clinical and Translational Research IND/IDE Consultation Team (I3CS). The I3CS Team has reviewed the proposed protocol and determined that the study is exempt from requiring an IND. This determination is based upon meeting the following requirements that are detailed in the FDA document *"Guidance for Clinical Investigators, Sponsors, and IRBs, – INDs – Determining Whether Human Research Studies Can Be Conducted Without an IND"*

The drug product is lawfully marketed in the United States.

The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication and there is no intent to use it to support any other significant change in the labeling of the drug.

In the case of a prescription drug, the investigation is not intended to support a significant change in the advertising for the drug.

The investigation does not involve a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2(b)(1)(iii)).

The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and with the requirements for informed consent (21 CFR part 50).

The investigation is conducted in compliance with the requirements of § 312.7 (i.e., the investigation is not intended to promote or commercialize the drug product)

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

A patient will be eligible for inclusion in this study if he or she meets all of the following criteria:

- Patient is between the ages of 18-70 years, inclusive.
- History of primary varicella infection (chicken pox)
    - Confirmed by a previous history of positive VZV IgG antibody or history of chicken pox
- Patient has a history of ulcerative colitis (UC) or Crohn's disease diagnosed by standard clinical, radiographic, endoscopic, and histopathologic criteria.

- Patient is receiving one of the following treatments for their IBD
    - Group A: Anti-TNF monotherapy (adalilumab, certolizumab, golilumab, infliximab)
    - Group B: Vedolizumab monotherapy
- Patient has been on stable treatment for IBD for at least three months.

5.2 Exclusion Criteria

A patient will not be eligible for inclusion in this study if he or she meets any of the following criteria:

- Previous receipt of any HZ vaccine
- Allergy to zoster vaccine or a component of it
- Other underlying chronic medical condition that could affect immunogenicity to vaccines (rheumatoid arthritis, etc.)
- History of herpes zoster or post herpetic neuralgia within the past year.
- Patient cannot or will not provide written informed consent.
- Patient is being administered immunomodulators currently or within the past three months
- Patient has been taking any dose of oral or intravenous steroids within 30 days prior to immunization.
- Patient has received polyclonal immunoglobulin therapy or blood products within the last year.
- Patient is pregnant per self-reporting
- Patient is older than age 70 years
- Unable to provide appropriate informed consent due to being illiterate or impairment in decision-making capacity.

5.3 Premature Subject Discontinuation

Patients will be encouraged to complete the study; however, they may voluntarily withdraw at any time at patient request.

If patients experience any of the following adverse events after the first dose of the vaccine they will be removed from the study and not receive the second dose: 1.) Allergic reaction to vaccine or 2.) Flare of IBD following immunization.

6.0 ELIGIBLE VACCINES

1. **Shringix**
    a. indicated for prevention of herpes zoster (shingles) in adults
2. **Drug storage and stability**

a. After reconstitution, administer SHINGRIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours

3. **Preparation, dosage, and administration of drug(s)**
    a. SHINGRIX is supplied in 2 vials that must be combined prior to administration.
    b. Intramuscular injection only.
    c. Two doses (0.5 mL each) administered intramuscularly according to the following schedule: A first dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later.
4. **Drug accountability procedures (if applicable; usually not required for drugs obtained through commercial venues and charged as standard of care)**
    a. N/A
5. **Concomitant medications allowed/disallowed, washout periods required**
    a. N/A
6. **Use of placebo and source of placebo**
    a. N/A
7. **Precautionary, prohibited medications and procedures**
    a. N/A
8. **Prophylactic medications and procedures**
    a. N/A
9. **Rescue medications**
    a. N/A
10. **Clinical or laboratory evaluations required**
    a. N/A

6.1 Formulation and Dosing

The herpes zoster subunit vaccine will be prescribed as recommended per standard of care guidelines by the patient's primary gastroenterology provider. The provider will speak with the patients about the risks and benefits of HZ immunization and only patients willing to receive the HZ vaccine will be provided the vaccine.

6.2 Vaccine Supply to Subject

All vaccines will be administered by nursing staff at the University of Wisconsin Hospital and Clinics.

7.0 STUDY ASSESSMENT SCHEDULE AND PROCEDURES

7.1 Subject Identification and Recruitment

Patients will be recruited from the University of Wisconsin Hospital and Clinics if they meet the inclusion and exclusion criteria (see **Sec 5.0**). Patients will be recruited in the following manner. Clinical research coordinators will prescreen providers' clinic schedules to evaluate

for potential study subjects that meet all inclusion criteria. The clinical research coordinator will review the potential patient with the primary gastroenterology provider prior to the patient's clinic visit. During the routine standard of care clinic visit, the primary gastroenterology provider will discuss the benefits of the standard of care Shingrix immunization with the patient, as per standard clinical practice. If the patient is interested in receiving the standard of care Shingrix immunization, the provider will also discuss the research study. If the patient is interested in participating in the study, the potential risk and benefits of study participation will also be discussed. Only those patients agreeing to receive the Shingrix vaccine and interested in the study will be approached by the clinical research coordinator to further discuss the study and the consenting process.

If a patient elects to participate in the study, patients will sign the consent form, enroll into the study, and perform the study assessments as described below.

Clinical research coordinators will be responsible for obtaining consent after the study has been reviewed with the patient's primary gastroenterologist and the patient. Patients who do not meet all inclusion criteria, or meet at least one of the exclusion criteria will not be recruited to the study.

7.2 Study Assessments by Visit

Baseline/Enrollment Visit (Day 0)

- Obtain written informed consent
- Assign Subject ID number
- Record demographics (gender, age, race and ethnicity)
- Collect medical history, including vaccination history and medications (ongoing and any medications taken during the last 30 days)
- Review inclusion and exclusion criteria to confirm eligibility
    - If patients do not have a history of chicken pox or medical history of chicken pox or a documented VZV result on file, the VZV IgG antibody test will be performed by the clinical laboratory to confirm varicella exposure. A blood sample of approximately 4mL (0.8 teaspoons) will be collected for this test. These patients will consent to the study and return to clinic at a later date to receive the vaccine and complete the baseline visit.
        - The VZV IgG sample will be resulted in the patient's medical chart.
- Complete Harvey-Bradshaw Index (HBI) or the Simple Colitis Activity Index (SCAI) questionnaire
- Collect a baseline blood sample of approximately 16 ml (3.2 teaspoons)
    - If the patient is receiving standard of care blood tests, these additional research samples will be collected at the same time as the standard of care tests.
- Receive the Shingrix vaccine as recommended by their gastroenterologist

- The vaccine will be administered as recommended per the packaging label.
- SHINGRIX is supplied in two vials that must be combined prior to administration. Prepare SHINGRIX by reconstituting the lyophilized varicella zoster virus glycoprotein E (gE) antigen component (powder) with the accompanying AS01B adjuvant suspension component (liquid). Use only the supplied adjuvant suspension component (liquid) for reconstitution. The reconstituted vaccine should be an opalescent, colorless to pale brownish liquid. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.
- Use a separate sterile needle and sterile syringe for each individual. The preferred site for intramuscular injection is the deltoid region of the upper arm.
- Adverse events: Immediate reaction to the vaccine were not seen in the clinical trial adverse events took a median duration of 2-3 days. The clinical research coordinator will call all patients at follow up day 12 and report all AE to PI at each site.

- Subjects will be instructed to contact the study team with any concerns or any development of fever, chills, rash or other concerning symptom.

Follow up Phone Call (approximately Day 12)

- Collect information to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physicians
- Provide reminder for follow up visit

Follow up Visit (approximately Day 60)

- Receive 2nd dose of herpes zoster subunit vaccine
- Complete Harvey-Bradshaw Index (HBI) or the Simple Colitis Activity Index (SCAI) questionnaire
- Collect information to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physician.

Follow up Phone Call (approximately Day 72)

- Collect information to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physicians
- Provide reminder for follow up visit

Follow up Visit (approximately Day 90, one-month post second dose of vaccine)

- Collect blood sample of approximately 16 mL (3.2 teaspoons)

  - If the patient is receiving standard of care blood tests, research blood samples will be collected at the same time as these standard of care tests.
- Complete Harvey-Bradshaw Index (HBI) or the Simple Colitis Activity Index (SCAI) questionnaire
- Collect information to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physician.

Follow up Visit (approximately Day 240, 6 months post second dose of vaccine)

- Collect blood sample of approximately 16 mL (3.2 teaspoons)
  - If the patient is receiving standard of care blood test, research blood samples will be collected at the same time as these standard of care tests.
- Complete Harvey-Bradshaw Index (HBI) or the Simple Colitis Activity Index (SCAI) questionnaire
- Collect information to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physician.

Follow up Visit (approximately Day 425, 12 months post second dose of vaccine)

- Collect blood sample of approximately 16 mL (3.2 teaspoons)
- Complete Harvey-Bradshaw Index (HBI) or the Simple ,Colitis Activity Index (SCAI) questionnaire
- Collect information to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physician.

7.3 Clinical Assessments

7.3.1 Blood Samples

All subjects participating in the study will have two blood specimens collected at four visits (days 0, 90, 240, and 425) for evaluation of humoral and cell mediated immunity to herpes zoster subunit vaccine. Subjects who do not have a history of chicken pox or a documented VZV IgG antibody result on file will have an additional blood draw collection to confirm previous exposure to the varicella virus. Humoral immunity will be measured using VZV antibody to ELISA and cell mediated immunity will be evaluated via ELISPOT.

Specimens at UW will be labeled with the subject's study ID number and date of collection so that data collected for this protocol can be linked to the sample. Samples will be stored in Rennebohm Hall at the University of Wisconsin. Only investigators and key personnel assigned to the laboratory have access to the lab. Samples will be coded (labeled with subject ID and date of collection) before they arrive to the lab. All computers used for data storage and analysis are password protected and used exclusively by key personnel.

All analysis on samples will be completed by UW staff.

Any future studies that will utilize these specimens will be done by UW researchers and will be submitted for a separate IRB approval. Only coded samples and data will be released for future research. The information linking the samples and data to individual subjects will not be released.

Varicella zoster antibody ELISA. Serum samples obtained prior to zoster vaccine administration, 90 days, 240 days and 425 days will be used to measure varicella antibody concentrations. Sera are being stored at –80ºC. These assays are done separately from the qualitative varicella zoster IgG clinical lab measurement to determine eligibility to participate in the study. Varicella antibody concentrations in serum samples will be measured using a commercially available ELISA kit (Abnova, Walnut, CA) according to the manufacturer's instructions. Although no correlation between varicella antibody concentration and protection from zoster has been identified, (22) the change in antibody concentration following immunization shows an immune response to the vaccine and is often included as a marker of zoster vaccine immunogenicity. (23)

Measure of Effect: ELISPOT and Antibody response *ELISPOT.* ELISPOT is an enzyme-linked assay for detecting and enumerating cytokine-producing lymphocytes. ELISPOT can detect cytokine-producing cells in as few as 1 in 300,000 cells. (24) ELISPOT is the standard for measuring varicella CMI and will be used to measure CMI on days 0, 90, 180 and 365. (25) Cytokine ELISPOT Sets for IFNγ (BD Biosciences, Pharmingen; San Diego, CA) will be used according to the manufacturer's instructions. All ELISPOTs will be performed in duplicate. Tetanus toxoid and phytohemagglutinin (PHA) (Sigma, St. Louis) will be used as positive controls. Two hundred thousand lymphocytes will be incubated with varicella zoster antigen, tetanus toxoid, PHA, or media alone (negative control) on IFNγ antibody coated plates at 37ºC for 48 hours. Cells will be washed away and labeled detection antibody added (biotin and avidin-horseradish peroxidase) followed by a chromogenic substrate. A colored spot indicates a cell producing IFNγ. Each well will be inspected and cytokine-producing cells will be counted using AID® imaging system. Any well with more than 300 spots will be considered too numerous to count and reported as >300 cells/well. ELISPOT will be repeated on these specimens starting with fewer cells.

7.3.2 Disease Activity Assessment

The Harvey-Bradshaw Index (HBI) or the Simple Colitis Activity Index (SCAI) questionnaire will be used to assess for CD or UC disease activity respectively (**Appendices 1 and 2**). These assessments include questions about patient overall well-being as well as specific symptoms and complications of CD or UC, such as stool frequency and abdominal pain.

Subjects will be questioned at each visit about their clinical symptoms and subsequently scored accordingly. The scores will be entered into the participant's medical record number.

7.3.3 Safety Assessments

Safety data collection for this study begins at the time the subject signs the informed consent. Safety assessments include questioning subject both at the follow up phone call and at the follow up visits bout Adverse Events and SAEs.

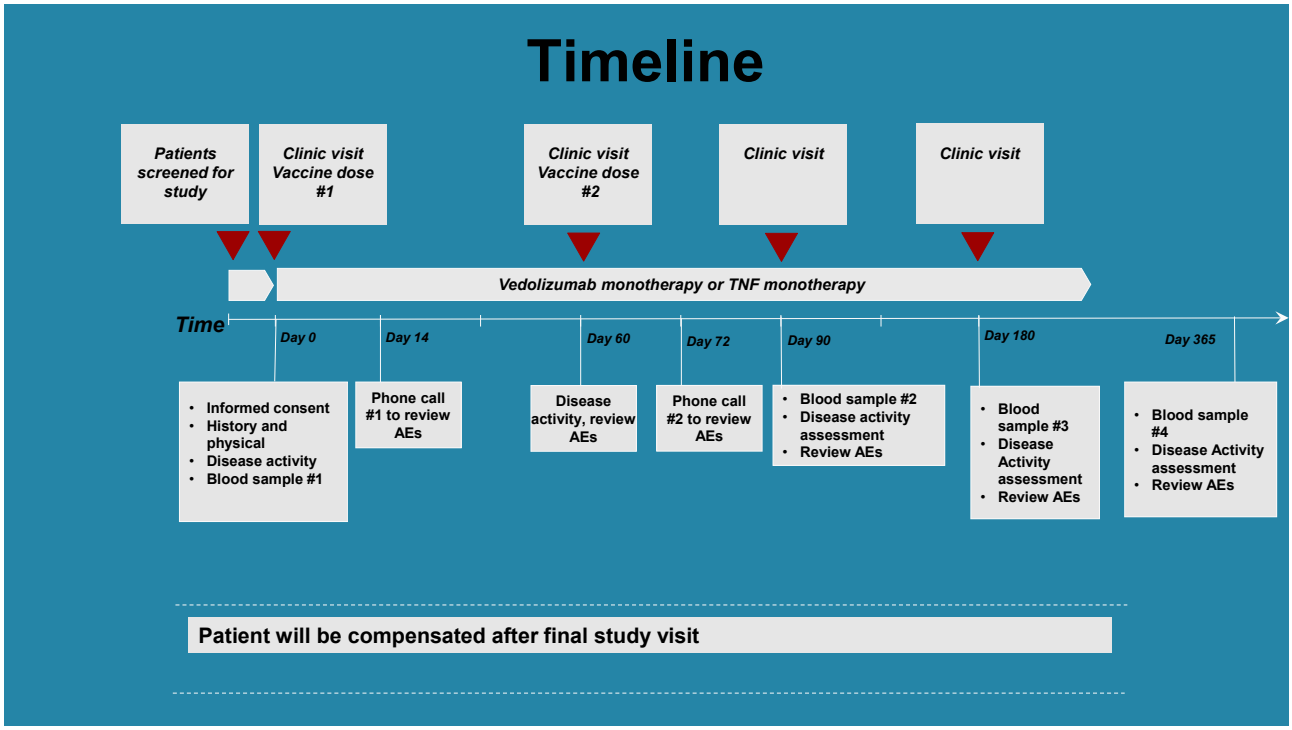
7.3.4 Other Measurements

A medical history will be obtained from the subject's medical records and entered into the research records. The medical history will include all diagnoses and other diseases.
A medication history must be present in the subject's medical records and be recorded in the subject research records; including all prescription medications and nonprescription therapies taken within 30 days prior to initial visit.

7.4 Study Duration

Major Study Periods	
First Patient In (FPI) to Last Patient In (LPI):	12 months
LPI to Last Patient Out (LPO):	14 months
LPO to manuscript	4 months

The study duration will be approximately 2 years. Each subject will be involved in the study for approximately 14 months.



8.0 SAFETY REPORTING

Safety Reporting

Institution/Investigator is solely responsible for reporting all Adverse Events and Serious Adverse Events to regulatory authorities, investigators, IRBs or IECs, GSK and Takeda, as applicable, in accordance with national regulations in the countries where the study is conducted.

Regardless of expectedness or causality, all SAEs and pregnancy reports must also be reported in English by facsimile to Takeda Pharmacovigilance or designee:

Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the sponsor-investigator's observation or awareness of the event

Takeda Safety Reporting Contact Information

Takeda requires that all information be communicated to Takeda's Pharmacovigilance Department as outlined in the study contract.

All reported adverse drug reactions and safety issues related to Takeda compound must be included in the final study report.

Definitions:

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline. We are mainly concerned of flares of disease immediately after vaccination at the blood sample # 2 visit.

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.
* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

Serious AE (SAE) means any untoward medical occurrence that at any dose:

1) results in death,
2) is life-threatening,
   Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

3) requires inpatient hospitalization or prolongation of present hospitalization,
4) results in persistent or significant disability/incapacity,
5) leads to a congenital anomaly/birth defect,
6) may require intervention to prevent one of 1)-5) above or may expose the patient to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee immediately. The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda Pharmacovigilance or designee will request this information from the sponsor-investigator. Please refer to study contract for Takeda pharmacovigilance contact information.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Takeda Pharmacovigilance or designee. Every effort should be made to follow the pregnancy for the final pregnancy outcome. Please refer to study contract for Takeda pharmacovigilance contact information.

Product Complaints and Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda and report the event.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not.

Individuals who identify a potential medication error situation should immediately contact Takeda (see below) and report the event.

Phone: 1-877-TAKEDA7 (1-877-825-3327)
E-mail: medicalinformation@tpna.com
FAX: 1-800-247-8860

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance.

9.0 LAB SPECIMENS AND FUTURE RESEARCH

After we have performed the tests for this study, we will keep any leftover blood for potential use in future research projects. Data created from the subjects' participation in this study will also be stored and locked in the GI Research Office. Although the specific future research using specimens is not known, the research will be related to the study of IBD and/or vaccine-related research.

Specimens will be labeled with the subject's study ID number and date of collection so that the data collected for this protocol can be linked to the sample. Samples will be stored in Rennebohm Hall at the University of Wisconsin. Only Investigators and key personnel assigned to the laboratory have access to the lab. Samples will be coded (labeled with subject ID and date of collection) before they arrive to the lab. All computers used for data storage and analysis are password protected and used exclusively by key personnel.

Any future studies that will use these specimens will be done by UW researchers and will be submitted for a separate IRB approval. Only coded samples and data will be released for future research. The information linking the samples and data to individual subjects will not be released.

10.0 CRITERIA FOR STOPPING OR CHANGING THE STUDY PROTOCOL

Should the Principal Investigator, FDA, Institutional Review Board of University of Wisconsin School of Medicine & Public Health become aware of conditions arising during the conduct of this study, such as flares of inflammatory bowel disease at a rate of 50% in the cohort post immunization, that may warrant the cessation of the study, cessation of the study will occur. Prior to such action, consultation between the Principal Investigator, and, as appropriate, the FDA and/or University of Wisconsin Health Sciences Institutional Review Board will take place.

11.0 APPENDICES

11.1 Appendix 1: Harvey-Bradshaw Index

Harvey-Bradshaw Index*

Patient sense of general well being in the last 24 hours

- ○ Very well (0 points)
- ○ Somewhat below normal (1 point)
- ○ Poor (2 points)
- ○ Very poor (3 points)
- ○ Terrible (4 points)

Patient report of abdominal pain in last 24 hours

- ○ None (0 points)
- ○ Mild (1 point)
- ○ Moderate (2 points)
- ○ Severe (3 points)

Number of liquid stools in last 24 hours

- ☐ Stools

Finding of an abdominal mass

- ○ No mass (0 points)
- ○ Possible mass (1 point)
- ○ Definite mass (3 points)
- ○ Mass present and tender (4 points)

Complications

- ☐ Arthralgias (1 point)
- ☐ Uveitis (1 point)
- ☐ Erythema nodosum (1 point)
- ☐ Aphthous ulcers (1 point)
- ☐ Pyoderma gangrenosum (1 point)
- ☐ Anal fissure (1 point)

- ☐ Newly discovered fistula (1 point)
- ☐ Abscess (1 point)

* Based on Harvey R, Bradshaw J (1980). "A simple index of Crohn's-disease activity.". *Lancet* **1** (8167): 514.

11.2 Appendix 2: Simple Clinical Colitis Activity Index

Simple Clinical Colitis Activity Index (SCCAI)

Sub score Category	**Scores**				
	0	**1**	**2**	**3**	**4**
Bowel Frequency (day)	1-3	4-6	7-9	>9	
Bowel Frequency (night)	0	1-3	4-6		
Urgency of defecation	None	Hurry	Immediately	Incontinence	
Blood in stool	None	Trace	Occasionally frank	Usually frank	
General well-being	Very Well	Slightly below par	Poor	Very poor	Terrible
Extra-intestinal manifestations (**arthritis, pyoderma gangrenosum, erythema nodosum, uveitis**)		1 per manifestation			

A maximum score of 19 points:

1) **Remission** = Score of **0 to 4** points
2) **Mild Activity** = Score of **5 to 7** points
3) **Moderate Activity** = Score of **8 to 16** points
4) **Severe Activity** = Score of **> 16** points

Walmsley RS, Ayres RC, Pounder RE, Allan RN. A simple clinical colitis activity index. Gut. 1998;43(1): 29-32.

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