Immunogenicity of herpes zoster subunit vaccine among ulcerative colitis patients treated with tofacitinib and other immunosuppressive regimens

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1 List of Abbreviations

Abbreviation	Abbreviation definition
CMI	Cell mediated immunity
ELISPOT	Enzyme linked immunospot
IBD	Inflammatory Bowel Disease
IFNγ	Interferon gamma
HZ	Herpes Zoster
SCCAI	Simple Clinical Colitis Activity Index
TNF	Tumor necrosis factor
UC	Ulcerative Colitis
VZV	Varicella Zoster virus

2 Protocol Summary

Title:	Immunogenicity of herpes zoster subunit vaccine in ulcerative colitis patients treated with tofacitinib
Population:	UC patients on one of four treatment regimens as standard of care, who receive the Shingrix VZV vaccine, 100 patients, male + female, ≥18 years old, no vulnerable populations
Intervention:	Each participant will be given two doses (0.5ml each) of the Shingrix vaccine, 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. The study population will generally include adult outpatient subjects with UC.
Objectives:	Change in CMI and VZV antibody concentration between pre-immunization and at 1 month and 6 months post-immunization. Also monitoring for vaccine adverse effects over this time.
Design/Methodology:	Observational study without randomization and 4 study arms: Tofacitinib (10mg by mouth twice daily) monotherapy VS Anti-TNF monotherapy (adalimumab, golimumab, infliximab) VS Anti-TNF therapy with a thiopurine (6-mercaptopurine or azathioprine) VS no therapy or 5-aminosalicylates. Blood samples collected at clinic visits at enrollment, 1 month post-immunization, and 6 months post-immunziation. If subject requires serologic confirmation of past VZV infection, an additional clinic visit 1 week after enrollment will be needed to follow-up on results of a confirmatory serology test.
Total Study Duration:	2 years.
Subject Participation Duration:	8-12 months.

3 Background/Rationale & Purpose

3.1 Background Information

Ulcerative colitis, a subset of inflammatory bowel disease, is a chronic inflammatory state of the gastrointestinal tract. Patients with IBD are at increased risk for developing infections including shingles with the Herpes Zoster virus as a result of their underlying disease regardless of immunosuppression. Studies have shown that those with IBD have an almost two-fold increased risk of HZ compared to age-matched controls[1]. Treatment with an immunosuppressant such as tofacitinib further increases this risk, as seen in patients with rheumatoid arthritis and psoriasis[2,3]. Since most IBD patients are treated with systemic immunosuppressants, 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.

Tofacitinib citrate (Xeljanz) is a Janus kinase inhibitor developed for the treatment of inflammatory diseases such as rheumatoid arthritis and psoriasis. The drug was approved in May 2018 by the FDA for the indication of moderate-to-severe UC but has been used off-label in various clinical settings. Shingrix is a new adjuvanted recombinant vaccine approved by the Food and Drug Administration for the prevention of herpes zoster in adults 50 years of age and older, and should be safe to administer in IBD patients. Though research has shown that patients with IBD on immunosuppression have an impaired immune response to vaccination as compared with non-immunosuppressed subjects and healthy controls[4], the data on efficacy using the Shingrix vaccine appears promising even in severely immunocompromised hosts[5].

Known risks include documented local and general reactions to the Shingrix vaccine as well as bruising or pain at the site of venipuncture. Potential benefits include vaccination to HZ as a result of receiving the Shingrix vaccine.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and BMC/BU Medical Campus Human Research Protection policies and procedures.

3.2 Rationale and Purpose

A study showing a lower risk of developing shingles in tofacitinib-treated patients who receive Shingrix will take years to complete. However, demonstrating a robust immune response to Shingrix may be used as a surrogate for a reduced risk of developing shingles and might alleviate prescribers' concerns regarding the use of tofacitinib.

This proposal will evaluate the immunogenicity of the new herpes zoster subunit vaccine in UC patients on tofacitinib monotherapy compared to those other therapies for UC. We will evaluate if the cell-mediated immunity to VZV is increased with immunization. Reactivation of VZV results in HZ, and strong cell mediated immunity prevents reactivation of HZ[6,7].

Our primary goal is to evaluate the immunogenicity of the herpes zoster subunit vaccine by obtaining pilot data to inform larger immunogenicity studies in the future. We will compare the VZV-specific T cell response (cell mediated immunity) prior and after immunization with the herpes subunit vaccine in IBD

patients aged 18 and older. T cell response is critical in preventing reactivation of VZV and will be measured using an IFNγ ELISPOT, the standard measure of CMI to VZV[8].

4 Objectives

4.1 Study Objectives

The primary objective of the study is to determine the immunogenicity of the herpes zoster subunit vaccine in ulcerative colitis patients on tofacitinib monotherapy compared to those on anti-tumor necrosis factor monotherapy, combination treatment with an anti-TNF agent and a thiopurine, and UC patients on 5-aminosalicylates or off therapy. Participants will be receiving the UC treatment regimens as standard of care prior to enrollment into the study. Immunogenicity will be evaluated by measuring humoral and cell mediated immunity in UC patients on tofacitinib who receive the two-dose herpes zoster vaccine. We will evaluate short term immunogenicity at one month after the second vaccination dose and sustained immunogenicity at 6 months post vaccination.

The central hypothesis of this proposal is that UC patients on tofacitinib will mount an adequate response to the Shingrix vaccine. We expect that the response will be slightly diminished compared to non-immunosuppressed IBD patients, comparable to those on anti-TNF monotherapy therapy and superior to those on anti-TNF therapy in combination with a thiopurine.

The immune response to the Shingrix vaccine has been shown to be >90% in healthy patients[9]. It is well-known that IBD patients on immunosuppression, especially combination therapy (TNF plus an immunomodulator), have an impaired immune response to vaccination as demonstrated by the prospective clinical trial by Melmed et al[4] and several others[10]. Therefore, we anticipate a diminished response to Shingrix in patients on TNF therapy in combination with a thiopurine. We are excluding patients receiving methotrexate as its utility in treating UC patients is limited. On the other hand, the response to inactivated vaccines in patients on anti-TNF monotherapy are conflicting in that some studies show a diminished response to the inactivated Hepatitis B vaccine[11,12] and the influenza vaccine[13] for instance where other trials showed an immune response that was comparable to healthy controls, in patients receiving tetanus and pertussis vaccinations[10]. Lastly, aminosalicylates are used to treat mild-to-moderate UC and have no effects on the immune system. While we recognize that this population differs from our study population, it is standard practice to include such patients in clinical trials as their response to vaccine is expected to be comparable to non-IBD patients and they serve as important controls. **Thus, we postulate that IBD patients off therapy or on 5-aminosalicylates, will respond most favorably to vaccination, followed by patients on anti-TNF monotherapy and lastly, patients on combination therapy with a thiopurine.**

With regard to tofacitinib monotherapy, the proportion of patients achieving vaccine response to PPSV-23 was lower in the tofacitinib group but may have been confounded by methotrexate[14]. The responses were 68.4%, 61.8 and 31.6% in the placebo group, tofacitinib monotherapy group and tofacitinib + methotrexate group respectively. In contrast, a similar proportion of patients receiving tofacitinib and placebo achieve adequate responses to the influenza vaccine. Another recent study showed that patients on tofacitinib 10mg BID demonstrate 60% response to the tetanus vaccine, defined as a 4-fold increase in antibody titers[15]. Similar response rates are seen in the IBD population on TNF-monotherapy[10]. IBD patients on tofacitinib will likely have failed biologic therapy and may be on short-

term steroids which may affect their immunogenicity to vaccines. **Thus, we anticipate that IBD patients on tofacitinib monotherapy will have a slightly diminished response to Shingrix compared to non-immunosuppressed IBD patients (or those on aminosalicylates) but that the response will be comparable to patients on anti-TNFs alone and superior to patients on combination treatment with a thiopurine.**

The secondary objectives of the study are to monitor for vaccine-related adverse events and change in UC disease activity throughout the duration of the study in order to obtain other practical information that may help inform providers in clinical decision making regarding the use of Shingrix and/or tofacitinib.

4.2 Study Outcome Measures

4.2.1 Primary Outcome Measures

Change in the immunogenicity of the herpes zoster subunit vaccine in UC patients. Immunogenicity will be assessed by the change in CMI as measured by ELISPOT from pre-immunization to 1 month after receiving second dose of booster vaccine post-immunization. ELISPOT is an enzyme-linked assay for detecting and enumerating cytokine-producing lymphocytes. 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. It will be measured from pre-immunization to 1 month after receiving second dose of booster vaccine post-immunization.

4.2.2 Secondary Outcome Measures

#1: **Sustained T cell response.** Sustained change in CMI at 6 months will be assessed after receiving a second dose of booster vaccine post-immunization.

#2: **Change in antibody response.** Antibody response will be measured by the change in VZV antibody concentration from pre-immunization to 1 month post-immunization. VZV antibody concentrations in serum samples will be measured using a commercially available ELISA kit (Abnova, Walnut, CA) according to the manufacturer's instructions. This quantitative VZV antibody concentration will be in addition to the one that may be needed to determine previous varicella infection for study eligibility.

#3: **Sustained antibody response.** Sustained change in VZV antibody concentration at 6 months after receiving a second dose of booster vaccine post-immunization will be assessed.

#4: **Vaccine adverse effects.** Patients will either receive phone calls from study personnel or be evaluated at clinic visits to ascertain vaccine-related adverse effects at months 1, 2, 3 (1 month post-immunization), and 8 (6 months post-immunization). Our study is underpowered to measure differences in adverse effects between groups. Adverse event data will be reported.

#5: **Change in UC disease activity.** The SCCAI will be used to measure disease activity. It is a questionnaire with six subscore topics with scores defined by UC signs and symptoms from 0 to 4 for a

range of scores from 0 to 17. Total scores are interpreted as: Remission = score of 0 to 4 points, Mild Activity = score of 5 to 7 points, Moderate Activity = Score of 8 to 16 points, and Severe Activity = Score of > 16 points.

5 Study Design

The clinical trial will be a Phase IV multi-center non-randomized non-blinded observational study. As part of standard of care for this patient population and therefore outside of the study, each participant will be given two doses (0.5ml each) of the Shingrix vaccine, 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.

The study population will include adult outpatient subjects with UC. The study will compare the immunogenicity and VZV antibody concentrations in the participants who will be stratified into one of 4 arms (each containing 25 subjects) based on their medical regimen, which is also standard of care and will be established outside of the study:

- Group A - UC patients on tofacitinib monotherapy.
- Group B – UC patients receiving anti-TNF monotherapy (adalimumab, golimumab, infliximab).
- Group C – UC patients on an anti-TNF agent and a thiopurine (6-mercaptopurine, azathioprine).
- Group D – UC patients on non-immunosuppressive therapy or 5-aminosalicylates.

As part of the actual study, 3 total blood samples will be collected. Samples will be collected at clinic visits at the time of enrollment, 1-month post-immunization, and 6 months post-immunization. Patients will also be asked to report change in their UC symptoms and any adverse effects to the vaccine at each clinic visit and follow-up phone calls.

6 Potential Risks and Benefits

6.1 Risks

The risks related to the research include bruising and pain at the site of venipuncture for blood draws. Baseline blood draw will be collected as part of their routine care visit and the blood draw at 1- and 6-months post-immunization are research-related blood draws that will be done by a trained phlebotomist.

In addition, the research carries a minimal risk of breach of confidentiality, with multiple safeguards in place to protect subjects' privacy. Gout and optic ischemic neuropathy are overall rare and not causally linked to the Shingrix vaccine; therefore, they are not noted as risks.

Additional risks that are part of standard of care and therefore not part of research include vaccine-related reactions. Risks from the Shingrix vaccine include injection site adverse events: pain (78.0%),

redness (38.1%), and swelling (25.9%). Other possible general adverse reactions include myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%).

Risks will be minimized by performing blood draws at the same time, when possible, as blood draws required for clinical care. Multiple safeguards, including a password protected computer to store the database, will be used to protect subjects' privacy.

Risks from the vaccine will also be mitigated by strict eligibility screening, which includes excluding subjects with a history of allergy to a zoster vaccine. At the time of obtaining informed consent, patients will be informed of the risks associated with the vaccine and will be provided a 24-hour number to study staff or the Gastroenterology fellow on-call for further management if reactions occur.

6.2 Potential Benefits

There are no direct benefits to subjects from participating in the study.

Societal benefits include providing data on the effectiveness of the Shingrix vaccine in patients on immunosuppressants. The data from this pilot study may be used to guide larger more powered studies in the future. The data from our study may also provide reassurance to patients and providers that that Shingrix is safe in a real-world setting for patients on immunosuppressants.

6.3 Analysis of Risks in Relation to Benefits

The risks of this study are minimal and are all sufficiently mitigated. While there is no direct benefit in this study, there are benefits to society. Therefore, with risks minimized, the risk to benefit ratio is favorable.

7 Study Subject Selection

7.1 Subject Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

- Age 18 or older
- Proof of primary varicella infection (chicken pox) either by appropriate history or, if history is atypical or mild, a positive VZV IgG antibody level
- Patient has a history of UC diagnosed by standard clinical, radiographic, endoscopic, and histopathologic criteria.
- Patient is receiving one of the following treatments for their UC
    - Tofacitinib monotherapy
    - Anti-TNF monotherapy (adalimumab, golimumab, infliximab)
    - Anti-TNF monotherapy plus a thiopurine (6 mercaptopurine, azathioprine)
    - No therapy or 5-aminosalicylates only if 50 years or older. (Individuals younger than 50 years, on no therapy or on 5-aminosalicylates will have to be immunosuppressed to fall under this category)

7.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Previous receipt of any HZ vaccine
- Allergy to zoster vaccine or a component of the vaccine
- Other underlying chronic medical conditions that are immunosuppressive or could affect immunogenicity to vaccines (HIV, transplant recipient on anti-rejection drugs, rheumatoid arthritis, psoriasis etc.)
- History of herpes zoster infection or post herpetic neuralgia
- Patient cannot or will not provide written informed consent
- Patient is on a non-licensed or experimental immunomodulator
- Patient is on methotrexate
- Patient is on steroids
- Patient has received immunoglobulin therapy or blood products with the past month
- Patient is pregnant or lactating

8 Study Intervention

The study intervention Shingrix is an adjuvanted recombinant vaccine approved by the Food and Drug Administration in 2021 for the prevention of herpes zoster in immunosuppressed adults 18 years of age and older. The vaccine is administered as two doses (0.5ml each) 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.

The Shingrix vaccine will be administered to subjects as part of their standard clinical care. The vaccine will be purchased with funding from Pfizer and be provided to subjects at no cost.

9 Study Procedures

See the Appendix for the schedule of events.

Patients with UC who meet the inclusion and exclusion criteria specified above, including being on one of four treatment modalities, will be recruited from the Center for Digestive Diseases at Boston Medical Center, the Hospital of the University of Pennsylvania, or the University of Wisconsin Hospital and Clinics. All 4 treatment modalities are standard of care and will have been established outside of the study.

Research staff, including a clinical coordinator, will generate a list of eligible patients and email the subjects' primary gastroenterologist (who is also a member of the research staff) the name and next appointment date of these patients. Patients will only be approached for recruitment at their next usually scheduled clinic appointment. A handout of the risks and benefits of the clinically indicated vaccine (Shingrix) will be given to each patient during their visit for their review. Patients will have the opportunity to opt in, opt-out, or defer from enrollment early in the consent process upon review of the handout. Because the vaccine is standard of care, patients will retain the opportunity to get the vaccine even if they choose not to participate in the study.

If a patient elects to participate in the study, he/she will sign the consent, be entered into the study, and complete the initial study assessments. If a patient elects to defer enrollment at the time of their clinic visit, he/she will be instructed to call the 24-hour phone number if he/she decides to enroll in the study at a later date.

All patient data, including demographic information and study assessments, will be collected and entered into REDCap, a secure electronic data capture system. This will ensure the confidentiality and integrity of the data throughout the study. Only authorized research personnel will have access to the REDCap database to maintain participant privacy and comply with data protection regulations.

Subject contacts:

#1 - Baseline/Enrollment Visit 1 (Day 0): Subjects will have a comprehensive medical history and physical exam performed, including vaccination history and all medications over the past 30 days. They will also complete an SCCAI questionnaire. A baseline blood sample of approximately 20mL (4 tablespoons) will then be obtained. If proof of past varicella infection is met by appropriate history, subjects will receive the Shingrix vaccine indicated based on their vaccination history as recommended by their gastroenterologist; otherwise subjects will follow-up in 1 week to review confirmatory serology results and receive vaccine if indicated. The Shingrix vaccine will be given in a two-dose series (0.5 mL each) administered intramuscularly –first dose at Month 0 followed by a second dose anytime between 2 and 6 months later. Subjects will be instructed to call the study team for any concerns or any development of fever, chills, rash or other concerning symptom.

#2- Follow up Visit 2 (approximately day 7): **This visit is only needed for patients who require serologic confirmation of past varicella infection, therefore patients who meet proof for past varicella infection by appropriate history do not require serologic confirmation and will NOT be scheduled for this visit.** Subjects will review results of the VZV antibody level test with their provider. If VZV antibody levels are positive, subjects will receive the Shingrix vaccine indicated based on their vaccination history as recommended by their gastroenterologist. Subjects will be instructed to call the study team for any concerns or any development of fever, chills, rash or other concerning symptom.

#3 - Follow up Phone Call 1 (approximately day 14): Subjects will receive a follow-up phone call to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physicians. They will also be reminded about their follow up visit.

#4 - Follow up Visit 3 (**approximately day 60, but can be up to day 180**): Subjects will complete a SCCAI questionnaire, and information will be collected to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physician. The 2nd dose of the Shingrix vaccine will be administered.

#5 - Follow up Phone Call 2 (approximately day 72): Subjects will receive a follow-up phone call to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physicians. They will also be reminded about their follow up visit.

#6 - Follow up Visit 4 (approximately day 90): Subjects will complete a SCCAI questionnaire, and information will be collected to identify any adverse effects including fevers or chills, rash, and visits to

the emergency room or to their primary care physician. A blood sample of approximately 20mL (4 tablespoons) will then be obtained.

#7 - Follow up Visit 5 (approximately day 240): Subjects will complete a SCCAI questionnaire, and information will be collected to identify any adverse effects including fevers or chills, rash, and visits to the emergency room or to their primary care physician. A blood sample of approximately 20mL (4 tablespoons) will then be obtained.

The entire procedure will be identically performed at the additional sites outside of BMC. The total study duration will be about 2 years, and the subjects' duration of participation will range from 8 to 12 months, depending on when the 2nd vaccine dose is administered.

Participants will receive a total of $50 in the form of reimbursement gift cards for their participation. A $20 gift card will be given at the time of enrollment, and a $30 gift card will be given at the 1-month post-immunization visit (follow-up visit 4).

All standard-of-care testing and procedures will be billed to the patient/patient's insurance. All initial research visits will be conducted as part of an already scheduled visit that the patient would be attending regardless of study participation; thus, the patient (or the patient's insurance) would cover the cost of this. At this visit, the patient will be vaccinated with a clinically indicated vaccine(s) that would be part of standard preventative care and have blood drawn. Patients with IBD generally have routine blood testing as part of their regular care. Given this, phlebotomy will be covered by the patient or their insurance, with the exception of the cost of the blood draws specifically for the research study (at follow up visits) which will be covered by research funding. The vaccine will be purchased with funding from Pfizer and be provided to subjects at no cost.

All blood samples will be processed (centrifuged, pipetted, and frozen) and stored at the research lab at BU/BMC medical campus located at 650 Albany Street Room 816. Upon finishing enrollment, blood samples (coded only with subject ID and exclude any identifiable private information) will be released outside of the BMC/BU Medical Campus only to co-investigator Dr. Freddy Caldera at the University of Wisconsin School of Medicine and Public Health. Samples will be stored and retained in a locked freezer until the end of the study.

If subjects wish to terminate their participation prior to the end of the study, they may do so by notifying their primary gastroenterologist or contacting the PI of the study via contact information included on their informed consent form.

10 Assessment of Safety and Data Safety Monitoring Plan (DSMP)

10.1 Definitions

The following definitions will be used in the assessment of safety:

Adverse Event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease,

temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Serious Adverse Event (SAE) is any adverse event that

(1) results in death;
(2) is life-threatening;
(3) results in inpatient hospitalization or prolongation of existing hospitalization;
(4) results in a persistent or significant disability/incapacity;
(5) results in a congenital anomaly/birth defect; or
(6) based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Life-threatening means that the event places the subject at immediate risk of death from the event as it occurred.

Unanticipated Problem is defined as an event, experience or outcome that meets **all three** of the following criteria:

- is unexpected; AND
- is related or possibly related to participation in the research; AND
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research

Unexpected means the nature, severity, or frequency of the event is not consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol–related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

10.2 Safety Review

Both the risks listed in Section 4.1 and unknown risks will be monitored as follows:

Research-related risks include bruising and pain at the location of blood draws. Patents will be monitored for these risks at the time of blood draw by the phlebotomist, at each clinic visit (enrollment as well as months 1, 2, 3, and 8) by their primary gastroenterologist, and via phone call (days 14 and 72) by research staff.

10.3 Reporting Plans

The Principal Investigator at BMC/BU Medical Campus will report Unanticipated Problems, safety monitors' reports, and Adverse Events to the BMC/BU Medical Center IRB in accordance with IRB policies:

- Unanticipated Problems occurring at BMC/BU Medical Campus involving a fatal or life-threatening event will be reported to the IRB within 2 days of the investigator learning of the event.
- Unanticipated Problems occurring at BMC/BU Medical Campus not involving a fatal or life-threatening event will be reported to the IRB within 7 days of the investigator learning of the event.
- Reports from safety monitors with recommended changes will be reported to the IRB within 7 days of the investigator receiving the report.
- Adverse Events (including Serious Adverse Events) will be reported in summary at the time of continuing review, along with a statement that the pattern of adverse events, in total, does not suggest that the research places subjects or others at a greater risk of harm than was previously known.
- Reports from safety monitors with no recommended changes will be reported to the IRB at the time of continuing review.

10.4 Stopping Rules

The study has no stopping rules.

11 Data Handling and Record Keeping

11.1 Confidentiality

All paper-based data will be filed in a locked cabinet for a minimum of 7 years after the end of the study, only accessible to the PI and co-investigators. All electronic information will be stored on a password protected computer in the GI section and numerically coded in a spreadsheet format, only accessible to the PI and co-investigators. Seven years after the completion of the study, all paper-based files will be destroyed by secure means and all computer data will be deleted. All patient data, including demographic information and study assessments, will be securely entered into REDCap, ensuring data confidentiality. Access to the REDCap database will be restricted to authorized research personnel for participant privacy and data protection compliance.

For urgent unanticipated problems, communication of information will occur over secured urgent emails followed by telephone calls among co-investigators and research staff. Among all three sites, scheduled conference calls will be held quarterly (roughly every 3 months) to discuss any interim results or protocol modifications.

The blood samples (coded only with subject ID and to exclude any identifiable private information) will be released outside of the BMC/BU Medical Campus only to co-investigator Dr. Freddy Caldera at the University of Wisconsin School of Medicine and Public Health and will be stored in a locked freezer until the end of the study.

The study's listing on ClinicalTrials.gov will be updated as needed to reflect any future changes in study protocol or results at the completion of the study.

The study monitor or other authorized representatives of the sponsor may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

11.2 Source Documents

Source documents include hospital records, clinical and office charts, and laboratory notes.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. Data may be transcribed legibly on CRFs supplied for each subject or directly inputted into an electronic system or any combination thereof.

11.3 Case Report Forms

The study case report form (CRF) will be the primary data collection instrument for the study. All data requested on the CRF will be recorded. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, "N/D" will be written. If the item is not applicable to the individual case, "N/A" will be written. All entries will be printed legibly in black ink. If any entry error has been made, to correct such an error, a single straight line will be drawn through the incorrect entry and the correct data will be entered above it. All such changes will be initialed and dated. There will be no erasures or white-out on CRFs. For clarification of illegible or uncertain entries, the clarification will be printed above the item, then initialed and dated. The following source data will be recorded directly on the CRFs: study ID, age, sex, race, subtype of UC, medical and surgical history including vaccinations, medication history, and adverse effects.

See the Appendix for the following CRFs:
1. Baseline visit data collection form
2. 2-month visit data collection form
3. 3-month visit (1-month post-immunization) data collection form
4. 8-month visit (6 months post-immunization) data collection form
5. Herpes zoster vaccine diary card
6. SCCAI form

11.4 Study Records Retention

All paper-based data will be filed in a locked cabinet for a minimum of 7 years after the end of the study, only accessible to the PI and co-investigators. All electronic information will be stored on a password protected computer in the GI section and numerically coded in a spreadsheet format, only accessible to the PI and co-investigators. Seven years after the completion of the study, all paper-based files will be destroyed by secure means and all computer data will be deleted.

Statistical Plan

11.5 Study Hypotheses

Our hypothesis is that at 1-month post-immunization, IBD patients on tofacitinib monotherapy will have a slightly diminished level of VZV-specific CMI from Shingrix compared to non-immunosuppressed IBD patients but that the VZV-specific CMI will be comparable to patients on anti-TNFs alone and superior to patients on combination treatment with a thiopurine.

Additional hypothesis:
At 6 months post-immunization, IBD patients on tofacitinib monotherapy will have a slightly diminished level of VZV-specific CMI from Shingrix compared to non-immunosuppressed IBD patients but that the VZV-specific CMI will be comparable to patients on anti-TNFs alone and superior to patients on combination treatment with a thiopurine.

At 1-month post-immunization, IBD patients on tofacitinib monotherapy will have a slightly diminished varicella antibody concentration from Shingrix compared to non-immunosuppressed IBD patients but that the varicella antibody concentration will be comparable to patients on anti-TNFs alone and superior to patients on combination treatment with a thiopurine.

At 6 months post-immunization, IBD patients on tofacitinib monotherapy will have a slightly diminished varicella antibody concentration from Shingrix compared to non-immunosuppressed IBD patients but that the varicella antibody concentration will be comparable to patients on anti-TNFs alone and superior to patients on combination treatment with a thiopurine.

11.6 Sample Size Determination

We will recruit a total of 100 subjects, anticipating 25 subjects per study arm. Assuming an attrition rate of 20%, our goal final sample size is 80 subjects, with 20 subjects in each arm.

Power calculations revealed that >200 patients per study arm would be needed to estimate small differences in efficacy, assuming a 10% difference between tofacitinib monotherapy patients and non-immunosuppressed IBD patients for instance. Since 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 various sites. Our goal is to perform exploratory data analyses and derive estimates of vaccine response results in this population to power future studies.

11.7 Statistical Methods

Summary statistics including the mean, median, SD and range will be presented for continuous variables and N (%) will be presented for categorical variables, overall and by IBD group. Comparisons across groups on baseline demographic and clinical characteristics will be performed using ANOVA for continuous variables and the chi-squared test for categorical variables. Any comparison across groups significant at the $p< 0.1$ level will be considered for a multivariable-adjusted model for the primary outcome.

For the primary outcome of percent change in cell-mediated immunity from baseline to one-month post-immunization, we will first compare the tofacitinib alone group (Group A) to the non-immunosuppressive group (Group D) using a contrast statement as part of an ANOVA model. Comparisons of Group A with Groups B and C will use the same methodology. The same methodology will be used to compare the secondary outcomes among the four IBD groups in a similar manner. Any imbalances in baseline characteristics will be incorporated into a multivariable regression model to determine the adjusted differences between groups.

Incidence of adverse events will also be compared between groups using the chi-squared or Fisher's Exact test, as appropriate. A value of $p< 0.05$ is considered statistically significant, except where otherwise noted.

12 Ethics/Protection of Human Subjects

This study is to be conducted according to applicable US federal regulations and institutional policies (which are based in federal regulations, guidance, and ICH Good Clinical Practice guidelines).

This protocol and any amendments will be submitted to the Boston Medical Center and Boston University Medical Campus IRB, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator. A copy of the initial IRB approval letter will be provided to the sponsor before commencement of this study.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The consent form will be submitted with the protocol for review and approval by the IRB. The consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. Consent will be documented as required by the IRB.

13 Literature References

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14 Appendix

Schedule of Events

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 those taken over past 30 days
- Conduct physical exam
- Review inclusion and exclusion criteria to confirm eligibility
- Complete SCCAI questionnaire
- Collect a baseline blood sample of approximately 20 ml (4 tablespoons)
- If proof of past varicella infection is met by appropriate history, subjects will receive the Shingrix vaccine indicated based on their vaccination history as recommended by their gastroenterologist; otherwise subjects will follow-up in 1 week to review confirmatory serology results and receive vaccine if indicated
- If administered vaccine, subjects will be instructed to call the study team for any concerns or any development of fever, chills, rash or other concerning symptom

Follow-up visit (approximately Day 7)

- **NOTE:** This visit is only needed for patients who require serologic confirmation of past varicella infection. Patients who meet proof for past varicella infection by appropriate history do NOT require serologic verification and therefore will not be scheduled for this visit
- If VZV antibody levels are positive (thus providing proof of past varicella infection), subjects will receive the Shingrix vaccine indicated based on their vaccination history as recommended by their gastroenterologist
- Subjects will be instructed to call the study team for any concerns or any development of fever, chills, rash or other concerning symptom

Follow up Phone Call (approximately Day 14)

- 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, but can be up to day 180)

- Receive 2nd dose of herpes zoster subunit vaccine
- Complete SCCAI 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)

- Collect blood sample of approximately 20 ml (4 tablespoons)
- Complete SCCAI 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)

- Collect blood sample of approximately 20 ml (4 tablespoons)
- Complete SCCAI 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.

Case report forms:
1. Baseline visit data collection form

1. Study ID:

2. Age _____

3. Sex
    a. Male
    b. Female

4. Race
    a. Caucasian
    b. Hispanic
    c. African American
    d. Asian
    e. Native American
    f. Other

5. Type of Inflammatory Bowel Disease
    a. Crohn's
    b. Ulcerative Colitis
    c. Indeterminate Colitis

6. Type of Ulcerative Colitis
    a. Proctitis
    b. Proctosigmoiditis
    c. Left sided disease
    d. Pancolitis

7. Crohn's Subtype per Montreal Criteria (12)
    a. A1 (<16), A2 (17-40), A3 (>40)
    b. L1 (ileal), L2 (colonic), L3 (ileocolonic), L4 (isolated upper disease)
    c. B1 (non-stricturing, non-penetrating), B2 (stricturing), B3 (penetrating)
    d. Perianal disease (YES or NO)

8. Previous surgical resection
    a. Yes/ No

        i. If yes
        ii. Ileal resection

iii. Total colectomy with ileal pouch anal anastomosis
iv. Colonic resection

9. Length of inflammatory Bowel Disease Diagnosis
    a. as official diagnosis in months_____

10. Disease activity
    a. Harvey Bradshaw score
        i. <8 remission
        ii. >8 active disease
    b. Partial Mayo UC score
        i. <2 remission
        ii. >2 active disease

11. Current Medications:

Current Medications	Dose (mg)	Freq	Length on med (mo)	Comments
Mesalamine				
Azathioprine or 6MP				
Methotrexate				
Anti-TNF Biologic (infliximab, adalimumab, certalizumab, etc.)				
Vedolizumab				
Tofacitinib				
Other:				
Other:				
Other:				
Other:				

12. Previous steroids in the past year
    a. _____

13. Dose and duration of steroid use in the past year
    a. _____

14. Previous IBD Medications

Past Medications	Dose (mg)	Freq	Dates on med	Length on med (mo)	Comments
Mesalamine					
Azathioprine or 6MP					
Methotrexate					
Anti-TNF Biologics (infliximab, adalimumab, certalizumab, etc.)					
Vedolizumab					
Ustekinumab					
Tofacitinib					
Mycophenolate					
Other:					
Other:					
Other:					
Other:					

15. Smoking status
    a. Never
    b. Former (include pack-years and quit year)
    c. Current (include duration, frequency, and quantity)

16. History of herpes zoster in the past?
    a. How long ago in months

17. Vaccination history: list or attach below

2. 2-month visit data collection form

1. Study ID: _____
2. Date of 1st herpes zoster vaccine: __/__/__
3. Date of 2 month visit blood draw: __/__/__
4. Current Medications:

Current Medications	Dose (mg)	Freq	Length on med (mo)	Comments
Mesalamine				
Azathioprine or 6MP				
Methotrexate				
Anti-TNF Biologic (infliximab, adalimumab, certalizumab, etc.)				
Vedolizumab				
Ustekinumab				
Tofacitinib				
Other:				
Other:				
Other:				
Other:				

Completed by:_____ Date: __/__/__

3. 3-month (1 month post-immunization) visit data collection form

1. Study ID: _____
2. Date of 2nd herpes zoster vaccine: __/__/__
3. Date of 1 month post-immunization blood draw: __/__/__
4. Current Medications:

Current Medications	Dose (mg)	Freq	Length on med (mo)	Comments
Mesalamine				
Azathioprine or 6MP				
Methotrexate				
Anti-TNF Biologic (infliximab, adalimumab, certalizumab, etc.)				
Vedolizumab				
Ustekinumab				
Tofacitinib				
Other:				
Other:				
Other:				
Other:				

Completed by:_____ Date: __/__/__

4. 8-month (6 months post-immunization) visit data collection form

1. Study ID: _____
2. Date of 2nd herpes zoster vaccine: __/__/__
3. Date of 6 month post-immunization blood draw: __/__/__
4. Current Medications:

Current Medications	Dose (mg)	Freq	Length on med (mo)	Comments
Mesalamine				
Azathioprine or 6MP				
Methotrexate				
Anti-TNF Biologic (infliximab, adalimumab, certalizumab, etc.)				
Vedolizumab				
Ustekinumab				
Tofacitinib				
Other:				
Other:				
Other:				
Other:				

Completed by:_____ Date: __/__/__

6. SCCAI form

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.