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Official Title: Evaluating the Safety and Efficacy of Deucravacitinib Compared to Placebo Hidradenitis Suppurativa (HS).

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PART B STUDY DESCRIPTION

TITLE OF PROTOCOL	A pilot study evaluating the safety and efficacy of deucravacitinib compared to placebo in the treatment of moderate-to-severe Hidradenitis suppurativa (HS)
Principal Investigator	Alexa Kimball, MD MPH

B1. PURPOSE OF PROTOCOL

A proof of concept study regarding the use of deucravacitinib in patients with HS may be a first step in elucidating and defining a definitive treatment for this chronic and potentially debilitating condition.

Objectives:

The objective of this study is to evaluate whether the TYK2 inhibitor, Deucravacitinib shows evidence of efficacy in the treatment of moderate-to-severe hidradenitis suppurativa. In order to evaluate this question we will use multiple previously published scoring systems to evaluate efficacy.

Primary Endpoint:

Change from Baseline in Inflammatory lesion counts (including combined counts of inflammatory nodules (N) and abscesses(A)/AN count) at week 16.

Secondary Endpoints:

- The population treatment effect on proportion of participants with Hidradenitis Suppurativa Clinical Response (HiSCR) at week 16 for the active treatment group relative to placebo without regard to IP compliance
- Changes in IHS4, Hurley Stage, Dermatology Life Quality Index (DLQI) scores, and Visual Analogue Scale (VAS) pain scores at week 16.
- Changes in HiSCR, IHS4, Hurley stage, DLQI, and VAS pain scores at weeks 4, 8, 12, and 16
- Change from baseline in draining fistula counts at week 16
- Changes in lesion counts (A, N, AN) at weeks 4, 8, and 12.
- Changes in ulceration at weeks 4, 8, 12, and 16
- Changes in AN count, HiSCR, IHS4, Hurley stage by clinical phenotype
- Change in clinical phenotype at week 16 compared to baseline

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

HS is a painful, chronic, skin disease characterized by recurrent inflamed nodules and abscesses and significant impact on patient quality of life. Although originally thought to be a disease of the apocrine glands, HS is now considered a disease of hair follicles, and more specifically, follicular occlusion. The exact etiology of HS remains obscure but is thought to be multifactorial.

HS affects women 2 to 5 times more than men and affects approximately 1% of the general population. Disease onset tends to occur during puberty, and prevalence decreases in postmenopausal females. A study comparing Dermatology Life Quality Index Questionnaire scores in HS to other dermatologic diseases found HS to have the greatest disease burden on patients' quality of life.

Treatment of hidradenitis suppurativa can consist of both medical and procedural interventions. Typical medical management, include topical and oral antibiotics and immunosuppressants, such as adalimumab. Procedural interventions are often undertaken in combination with medical therapy and may be employed when medical management alone fails to prevent and/or clear HS lesions.

Over the past few years, clinical and research interests in HS has skyrocketed, but the literature still lags behind. One of the main difficulties in treating HS is its heterogeneous presentation. Multiple clinical phenotypes have been described, but the relevance of these phenotypes is still uncertain. The first and only drug approved for treatment of moderate to severe Hidradenitis suppurativa is adalimumab, which was approved in 2015. Yet evaluating the data from the Phase 3 trials for adalimumab, successful response was defined as >50% improvement in lesions, and this only occurred in about 50% of patients. Moreover, a gap still exists for evidence-based therapy of moderate-to-severe HS disease.

The inflammatory cytokines involved in HS are still somewhat unclear. There is evidence that inflammation may be associated with TNF-alpha, IL-1, IL-6, IL-17, and IL23. Thus, targeting these cytokines may modulate disease activity. TYK2 is a ubiquitous tyrosine kinase, transducing signals of immunoregulatory cytokines acting on a variety of immune and non-immune cells. It is a critical signal transduction kinase in the JAK-STAT pathway and is particularly relevant to the pro-inflammatory receptors for IL-23, IL-12 and type I IFNs. It plays a vital role in some immune processes, including natural killer (NK) cell activity, B-cell maturation and differentiation of Th1 and Th17 cells. In an uncontrolled, open-label, investigator-initiated study of ustekinumab (IL12/23 inhibitor) administered at 45 or 90 mg at weeks 0, 4, 16, and 28 (weight-based dosing), an improvement in the modified Sartorius score was achieved in 82% of patients at week 40. Additionally, forty-seven percent of subjects achieved a HiSCR response. This study suggests that deucravacitinib may be a therapeutic agent in HS disease management.

Recent literature as described above suggest a possible role for TYK2 inhibition as a potential therapeutic strategy in patients with HS. Oral deucravacitinib is a tyrosine kinase 2 (TYK2) inhibitor that binds to the pseudokinase domain of the enzyme and is functionally more selective than other tyrosine kinase inhibitors. Tyrosine kinase 2 (TYK2), an intracellular signaling enzyme, activates signal transducer and activator of transcription (STAT)-dependent gene expression and functional responses of interleukin-12, interleukin-

23, and type I and III interferon receptors. These cytokine pathways are involved in the pathologic processes associated with immune-mediated disorders, including psoriasis. TYK2 inhibition blocks activation of signal transducers and activators of transcription (STAT) factors causing down regulation of the innate immune response. Deucravacitinib, a member of the TYK-2 inhibitor class, has recently shown excellent results in psoriasis, and our group has also reported on the efficacy of tofacitinib, a JAK inhibitor that also affects the STAT pathway, in a case series of severe complicated HS patients. Given the evidence of general efficacy, known safety profile and opportunity to treat HS with a more broadly effective medication, we propose testing the anti-inflammatory effect of deucravacitinib in HS.

A proof of concept study regarding the use of deucravacitinib in patients with HS may be a first step in elucidating and defining a definitive treatment for this chronic and potentially debilitating condition.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Study Design:

This study is a randomized, proof of concept study. 30 patients aged 18 and over with HS will be included in this single center, randomized, double-blind, parallel-group study. Dosage of deucravacitinib will be given according to the investigational regimen as follows: 6 mg po bid for 16 weeks. The study comprises a 4-week screening period, a 16-week study period, and a 4-week follow-up period. The follow-up period consists of a follow-up phone call 4 weeks after the last study drug dose.

Dosage

Subjects will be randomly assigned to receive either deucravacitinib or placebo. Dosage of Deucravacitinib and Placebo will be given according to the following regimen:

- Deucravacitinib group: 6 mg po bid x 16 weeks
- Placebo group: 1 tablet po bid x 16 weeks

Study Drug	Frequency of Administration	Route
Deucravacitinib 6 mg	1 active tablet in the morning and evening (BID)	Oral
Placebo	1 inactive tablet in the morning and evening (BID)	Oral

Randomization, blinding and treatment allocation

Subjects will be randomized 2:1 to study drug or placebo. All subjects assigned to study drug will receive study drug for a total of 16 weeks. Subjects assigned to placebo will receive 16 weeks of placebo. The investigator and the subject will remain blinded to each subject's initial treatment throughout the study.

A paper randomization will be used for the study due to the small sample size and no stratification based on disease severity will be performed. An unblinded container file associated with batch drug shipment will be sent to unblinded research pharmacist at BIDMC by the study sponsor.

We will work with a biostatistician to create an unblinded randomization log using computer generated block randomization, this will also be directly sent to the research pharmacist. Unblinded pharmacist will create a blinded log for the research team and since they are not available 24/7, they will create Emergency Code Breakers (sealed envelopes with subject treatment assignments) that will be held by the blinded research team incase there is a need for emergency un-blinding.

Medication will be dispensed during scheduled study visits by study personnel. Subjects will take drug at home and record compliance in a daily diary. It is recommended that the first dose of study drug be taken by the subject while the subject is at the site.

Overview of study procedures

	Screenin g	Baseline	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20 followup Call
Informed Consent	X						
Inclusion/ Exclusion	X	X					
History/ Demographics	X						
Targeted Physical Examination	X					X	
HS Assessments	X	X	X	X	X	X	
Labs: CBC, BMP, LFTs, CPK		X	X			X	
Hep B and C screening	X						
TB screening	X						
HIV screening	X						
ESR, CRP		X	X			X	
Photographs (optional)		X	X	X	X	X	
Urine Pregnancy Test*	X	X	X	X	X	X	
PROs: DLQI, Pain Assessment		X	X	X	X	X	
Con Meds/ Adverse Events		X	X	X	X	X	X
Randomization		X					
Medication Administration		X	X	X	X		
Medication Dispensation		X	X	X	X		
Review of patient drug diary		X	X	X	X	X	

*for women of childbearing potential only

Study Procedures

Prior to performing any study related procedures, the investigator will discuss with each subject the nature of the study, its requirements and its restrictions. A written informed consent form will be obtained from each participant prior to any procedure. Each subject with a signed informed consent form will be screened at the first visit, to ensure all the inclusion criteria are met and none of the exclusion criteria. Study procedures are described in detail below and an overview of the study procedures during each visit can be found in the chart.

Informed Consent

Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed, signed, and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Medical history

- A complete medical history will be taken at screening. The subject's medical history will be updated at the Baseline visit. This updated medical history will serve as the baseline for clinical assessment.
- Demographic information, including subject self-reported gender, race, age, ethnicity, and child-bearing potential will be recorded.
- Nicotine and alcohol history will be obtained

HS history: Date of onset of HS, all previous and current medical and procedural treatments for HS, and reasons for discontinuation or outcomes of previous treatments will be obtained.

Targeted Physical exam, including height and weight and vital signs

Height will be measured at screening only. Body weight will be measured at all scheduled visits. The subject will wear lightweight clothing and no shoes during weighing.

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

A targeted physical examination, including cutaneous examination to evaluate for skin malignancies, will be performed at the designated study visits. The physical examination will be performed at screening and week 16. If appropriate, a targeted physical exam should be performed at any other visit (e.g., to evaluate a reported adverse event). Any significant physical examination findings after the first dose will be recorded as adverse events, while any findings prior to the first dose will be recorded as medical history. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate AE report form. At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

Efficacy assessment: Lesion counts will be performed by the investigator at each study visit. Patient-reported outcomes, including DLQI and Pain score, will be administered to subjects as subject questionnaires prior to any assessment of disease severity or laboratory testing.

Photography (optional) Subjects will be given the option to have digital photographs taken of their HS lesions according to the study procedures table. Written consent will be obtained and documented on the Informed Consent Form .

Photos will be taken with an iPad approved by Beth Israel Deaconess Medical Center IS Support team. Photos will be stored for at least 6 years. All photos will be stored without identifiers and coded with unique subject ID. No readily identifying photos/images or information will be disclosed. Identifying aspects such as tattoos, moles, skin tags might be visible in the photo. These photos / images or parts of them may be used for publication and/or education. If so, subject identity will not be disclosed.

Laboratory Testing

Blood samples will be collected at scheduled visits. A certified laboratory at Beth Israel Deaconess Medical Center (BIDMC) or Quest Diagnostics will be utilized to process and provide results for the clinical laboratory tests. Laboratory samples will be obtained in the Clinical Research Center (CRC) at BIDMC.

Laboratory reference ranges will be obtained prior to the initiation of the study. The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

Whether action needs to be taken to address notable laboratory values will be decided by the investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.

The following laboratory tests will be performed according to the study procedures schedule:

- Complete Blood Count (CBC): automated WBC, RBC, hemoglobin, hematocrit, platelet count and RBC indices
- Basic Metabolic Panel (BMP): Sodium, Potassium, Chloride, Bicarbonate, BUN, Creatinine, Glucose
- Liver Function Tests(LFTs): Alk Phos, ALT, AST, Total Bilirubin, GGT
- HIV: HIV1&2 Antibody/Antigen Combo Assay
- Hepatitis B: Hep B Core Ab (Hep B Cab), Hep B Surface Antigen (Hep B Sag), and Hep B surface antibody (Hep B Sab)
- Hepatitis C: Hepatitis C antibody
- Tuberculosis: Quantiferon-TB Gold or T-spot
- Erythrocyte Sedimentation Rate (ESR)
- C-reactive Protein (CRP)
- Creatine Phosphokinase (CPK)
- Urine pregnancy testing for women of childbearing potential

Assessment

We will assess the proportion of subjects achieving improvement based upon the achievement of HiScr or change in Hurley Stage, DLQI, or VAS pain score as compared to baseline visit. Differences will be assessed at weeks 4, 8, 12, and 16 (as compared to minocycline). We will assess the average change in inflammatory lesion count per subject following 4, 8, 12, and 16 weeks of treatment as compared to baseline. Inflammatory lesions are defined as inflammatory nodules or abscesses.

The number and proportion of participants who achieve a HiSCR at Weeks 16 will be summarized and compared to placebo. HiSCR is a validated, binary outcome and is

defined as at least a 50% reduction from baseline in the total abscess and inflammatory-nodule count, with no increase in the abscess or draining fistula count.

HiSCR Assessment

Relative to baseline, all three criteria must be met.

- 1. >50% reduction in the total number of inflammatory nodules and abscesses**
- 2. No increase in abscess count**
- 3. No increase in draining fistula count**

Hurley Staging is a surgical staging system used to describe disease severity. No improvement in Hurley scoring is expected with medical management alone. Pre- and post-study drug scores will be compared.

Secondary exploratory endpoints include change in ulceration and change in overall disease severity by clinical phenotype. No current scoring system exists in HS for ulcerations. Subjects with ulceration present at baseline visit will be assessed for change in ulceration number by anatomical region or size (>25% decrease, >50% decrease, 75% decrease, >90% decrease). Additionally, clinical phenotype of subject (Follicular nodular phenotype vs. infiltrating phenotype vs. comedonal phenotype vs. ulcerating phenotype) will be identified at baseline. Subjects will be reassessed every 4 weeks to identify any shifts in phenotype with therapy. At week 16, descriptive subanalysis will be performed to identify any clinical phenotypes that are more or less likely to respond to TYK2 inhibition.

Patient-Reported Outcomes

Pain Score

A Pain Score will be calculated based upon a 10-point visual analog pain scale, which has been widely used to rate pain in both children and adults and has also been used in dermatology clinical trials. Response based on an improvement from baseline at all scheduled time points will be calculated. We will compare pre and post treatment pain values and categorize patients as

- (i) Resolved
- (ii) Improved
- (iii) Stable
- (iv) Worsened

Dermatology Life Quality Index (DLQI)

A Quality of Life Score will be calculated based upon the Dermatology Life Quality Index (DLQI).

The DLQI is a validated general dermatology questionnaire that consists of 10 items that assess subject health-related quality of life (daily activities, personal relationships, symptoms and feelings, leisure, work and school, and treatment). It has been extensively used in dermatology clinical trials for AD. The DLQI is a psychometrically valid and reliable instrument that has been translated into several languages, and the DLQI total scores have been shown to be responsive to change. The minimally important difference for the DLQI has been estimated as a 2 to 5 point change from baseline.

Rescue Treatment

Rescue treatment defined as Intralesional Kenalog (ILK-10) and Incision and Drainage (I&D) will be allowed at discretion of the Investigator of up to 2 procedures during the course of the study. If greater than 2 procedures are required during the length of the study, the subject will be discontinued. The lesion that was treated will be carried forward as active for the purpose of statistical analysis.

Follow up phone call at Week 20

Study personnel will call subjects to collect information regarding the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs since last study visit.

Early Termination Visit: If a subject is withdrawn from the study for any reason, including withdrawing informed consent, he/she will be asked to return for an early termination visit within 2 weeks of being withdrawn from the study. Procedures performed at Early Termination Visit will be identical to Week 16 visit.

An overview of the exact procedures during each visit can be found in the chart.

Confidentiality

All information generated in this study will be considered highly confidential and will not be disclosed to any persons not directly concerned with the study. Subjects will only be identified at a minimum by unique subject numbers in the study database.

Management of Reporting of Adverse Events**Adverse Events and Serious Adverse Events****Adverse events (AEs)**

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug 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 causal relationship can be one of the following:

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.

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

Adverse Events of Interest (AEIs)

Adverse events of interest (AEIs) are AEs for a particular product or class of products that a Sponsor may wish to monitor more carefully. AEIs may be serious or non-serious and may require further investigation to better characterize and understand them. In the BMS deucravacitinib clinical development program, select infections (opportunistic, TB, herpes

zoster) and malignancies have been identified as AEs based on the mechanism of action of deucravactinib. Therefore, in order to better characterize and understand these AEs, information may be collected on supplemental CRFs at the request of the sponsor. Additionally, information on potential AEs based on the disease or population under study may be collected on supplemental CRFs at the request of the sponsor.

Serious Adverse Events (SAEs)

A NON-SERIOUS ADVERSE EVENT is an AE not classified as serious.

SERIOUS ADVERSE EVENTS

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant 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)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

All SAEs will be reported to IRB within 24 hours after taking knowledge of the events as outlined by the Beth Israel Deaconess Medical Center Committee on Clinical Investigations (CCI/IRB) "Reportable Event" guidelines. SAEs will also be reported to the funding agency, Bristol Meyers Squibb. Although pregnancy and potential drug-induced liver injury (DILI), are not always serious by regulatory definition, these events will be reported within the SAEs timeline.

Additionally, any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) will be used to report SAEs to BMS. The BMS Protocol number will be included on the SAE form or on the cover sheet with the SAE form transmission.

The CIOMS form is available at: <https://cioms.ch/cioms-i-form/>

The MedWatch form is available at: <https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting>

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1-609-818-3804

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 \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

Follow-up of Adverse Events

The Investigator will follow adverse events until the time the adverse event either ceases permanently or is clinically stabilized. All adverse events will be reported according Beth Israel Deaconess Medical Center CCI/IRB guidelines.

NON-SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The collection of non-serious AE information will begin following the subject's written consent to participate in the study. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.

SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any follow-up protocol-specified procedure (eg, a follow-up skin biopsy).

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The Investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.

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

- If the Investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Site Monitoring Plan

Site has appointed a member of the study team to act as monitor for this protocol. Assigned monitor will review regulatory binder after initial IRB approval is received. Interim review will occur every two weeks after first patient is enrolled in the study until last patient visit has occurred. Assigned monitor will review regulatory binder, subject binders which include signed ICFs and paper CRFs, returned drug accountability log maintained by study staff. Monitor will use CCI template to generate a monitoring reports after each visit.

Expedited and periodic safety update reporting by BMS:

In accordance with local regulations, BMS will notify Investigator of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of either a SUSAR Report or a Semi-Annual SUSAR Report. Investigator (or delegate) will receive these reports through the FastTrack portal.

Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or Investigator or BMS decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the Investigator must review and retain the ESR with the IB. The Investigator will submit the ESR to the BIDMC CCI/IRB with the annual continuing review or sooner per "Reportable Event" guidelines. The investigator and CCI/IRB will determine if the informed consent requires revision. The investigator will also comply with the CCI/IRB procedures for reporting any other safety information.

Withdrawal of individual subjects

Subjects are free to leave the study at any time for any reason without any consequences. The investigator can decide to withdraw a subject from the study, due to urgent medical reasons. Other criteria for withdrawal of a subject are listed below:

- Changes in the patients' medical status that lead to a compromised safety of the patient or no longer meeting all the inclusion criteria.
- Serious adverse events
- Serious or acute illness or worsening of a current illness
- Protocol violations, such as non-compliance to study procedures and subject lost to follow-up.

Replacement of individual subjects after withdrawal

If possible, a subject will be replaced after another subject is withdrawn.

Follow-up of subjects withdrawn from treatment

If needed, appropriate care will be arranged for patients that drop out of the study.

Premature termination of the Study

The following criteria will determine premature termination of the study:

- Serious safety concerns
- Falsification of data

When this situation occurs, subjects should be seen on a short notice and be provided with suited medical care or be referred to an appropriate physician.

B. Statistical Considerations

Sample Size Justification:

A total enrollment of 30 subjects (20 study drug, 10 placebo) is anticipated in this single-center, randomized, double-blind, parallel-group study. This study is powered (based on a two-sample t-test) to show a significant difference in efficacy of treatment using the following assumptions based on other clinical trials: baseline average inflammatory lesion count of 12, improvement of 7 in the treatment group and 3 in the placebo group, with a power of 0.87, SD of 3.25 and alpha level of 0.05. The HiSCR will be a secondary endpoint (reduction of inflammatory lesions by 50% with no increase in fistulas or abscesses).

Data Analysis:

Primary study parameter(s)

Primary Endpoint: The clinical efficacy will be measured by change in lesion count versus placebo

The statistical analysis will be performed using SAS® Version 9.4. Patient characteristics and demographic data will be presented using descriptive statistics; mean, median, SD for continuous variables and for categorical variables frequency and percentages.

Primary End point: Change from Baseline in AN count at week16: A linear mixed effects model for repeated measures analysis will be used the change from Baseline in AN count to Week 16.

Secondary study parameter(s)

Secondary endpoints: Secondary endpoints will be measured using scoring tools

The population treatment effect on proportion of participants with HiSCR at week 16 for the active treatment group relative to placebo without regard to IP compliance: The population-based treatment effect will be the differences in the proportions of success in each treatment arm compared to the combined placebo

Percent change from baseline in HS Pain NRS at Week 16 : Analysis will be based in ANCOVA if parametric data set and Wilcoxon signed rank test if non-parametric
Change from Baseline in IHS4, draining fistula count, Hurley Stage, Dermatology Life Quality Index (DLQI) scores, and Visual Analogue Scale (VAS) at week 16.: Analysis will be based in ANCOVA if parametric data set and Wilcoxon signed rank test if non-parametric

Other study parameter(s)

Full analysis set will consist of all participants who received at least 1 dose of IP and had a valid baseline measurement and a post-baseline measurement for lesion count.

C. Subject Selection

Inclusion Criteria

A subject must meet all of the following criteria in order to be eligible to participate in this study:

- Male or Female at least 18 -70 years of age
- Able to provide informed consent
- Have at least 5 abscesses and/or inflammatory nodule (AN) count at baseline visits
- Have HS lesions in 2 distinct anatomical areas
- Women of Childbearing potential must have a negative serum urine pregnancy test at screening and a negative urine pregnancy test at baseline -- prior to administration of the first dose of study medication • Women of childbearing potential must be willing to continue a highly effective method of birth control throughout the study (oral, injected or implanted hormonal methods of contraception; placement of an intrauterine device or intrauterine system; barrier methods: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal foam/gel/film/cream/suppository (if available in their locale); male partner sterilization (the vasectomized partner should be the sole partner for that participant); true abstinence (when this is in line with the preferred and usual lifestyle of the participant).
- Tuberculosis Screening
 - o Negative IGRA screening for tuberculosis within 3 months prior to screening or those with a negative IGRA test performed at the screening visit, OR
 - o If a positive history of latent tuberculosis:
 - Currently receiving treatment for latent TB per standard of care (with at least 4 weeks of treatment prior to baseline visit)
 - Have documentation of having completed treatment within 5 years prior to baseline
- Agree not to have a live vaccination during the study

Exclusion Criteria

Eligible subjects will be excluded from participation if they meet any of the following criteria:
Exclusion Criteria:

- Any other active skin disease that in the opinion of the investigator would interfere with the assessment of HS
- Have greater than 20 draining fistula at baseline
- Receipt of non-biologic treatments for HS within 4 weeks prior to baseline other than antibiotics or hormonal therapy
- Receipt of TNF agents (i.e. Infliximab, adalimumab) or other biologics within 6 weeks prior to baseline
- Receipt of new hormonal therapy for HS within 3 weeks prior to baseline
- Receipt of oral antibiotics within 3 weeks prior to baseline. NOTE: subjects on concomitant antibiotics with a stable dose for 4 weeks prior to baseline visit may be included in the study. Only 25% of total enrollment may be on concomitant antibiotics.
- Receipt of intralesional kenalog injections within 2 weeks prior to baseline

- Receipt of topical steroids or topical antibiotics for HS for 2 weeks prior to baseline o NOTE: subjects may continue topical washes (benzoyl peroxide, chlorhexidine, zinc pyrithione, dilute bleach)
- Receipt of opioid analgesics or other concomitant analgesics for HS pain within 72 hours prior to the baseline visit
- Any uncontrolled diagnosis or condition that in the opinion of the investigator will interfere with the assessments or the study.
- Currently has a malignancy or a history of a malignancy within 5 years before screen (except successfully treated non-melanoma skin cancer or cervical carcinoma in situ)
- History of an ongoing, chronic or recurrent infectious disease
- Are currently pregnant, breastfeeding, or planning to get pregnant during the study o male participants who are actively trying to conceive with their partner are also excluded.
- Previous hypersensitivity reaction to deucravacitinib or to any of the components
- Known allergy to tetracycline antibiotics
- Known infection with HIV, hepatitis B or hepatitis C at screening or randomization. Patients who are Hepatitis B Core antibody and/or Hep B Surface Antigen positive will be excluded from this study. Patients who are Hepatitis C ab positive will also be excluded from this study.
- Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal) which in the opinion of the investigator significantly immunocompromises the subject and/or places the subject at unacceptable risk for receiving an immunomodulatory therapy

Women of Childbearing Potential

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment. Effective contraception is defined as one of the following:

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) associated with inhibition of ovulation
- Progestogen-only hormonal birth control (oral, injectable, transdermal) associated with inhibition of ovulation
- Bilateral tubal occlusion/ligation • Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS).
- Vasectomized sexual partner(s) (the vasectomized partner should have received medical assessment of the surgical success and is the sole sexual partner of the trial participant).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

B4. POSSIBLE BENEFITS

There will be no benefit to subjects who participate in the study. However, in the future, others are expected to benefit from the findings of this study.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO**More Common [>5% occurrence]**

- ☐ upper respiratory infections (URI), including Nasopharyngitis ("common cold")

Less Common [>1% but <5% occurrence]

- ☐ Increase in creatinine phosphokinase (a type of protein from muscles) in the blood,
- ☐ herpes simplex infection, (i.e., "Cold sores")
- ☐ mouth ulcers,
- ☐ folliculitis (infection of hair follicles)
- ☐ acne

Rare [<1% occurrence]

- ☐ herpes zoster infection, also known as "shingles"
- ☐ Diarrhea
- ☐ Nausea
- ☐ Cancer

Summary of known and potential risks and benefits

Deucravacitinib (SOTYKTU) has been studied extensively in both "Phase 2 and Phase 3 studies" for its use in psoriasis. These are required studies before bringing a medication to patients. The Phase 2 study had a smaller number of patients but assessed multiple doses (including the 6mg twice daily [BID] dose which this current study is using, in hidradenitis suppurativa). The Phase 3 studies had roughly 1700 patients and assess the dose of 6mg daily for psoriasis. You should discuss any side effects that may arise with the study team/your doctor immediately.

In the Phase 2 study, adverse events were reported in 51% of the patients in the placebo group and 55 to 80% of the patients in the active-drug groups, with the highest percentage in the group receiving 6 mg twice daily. There was a higher occurrence of mild-to-moderate acne in the active-treatment groups than in the placebo group, with 4 cases (9%) in the highest-dose group.

Infections, including Tuberculosis

In psoriasis patients who take medications which act on the immune system (such as deucravacitinib) infections are often experienced. These tend not to be severe, and tend to resolve on their own. However, sometimes serious infections may occur. It is important that you inform your doctor of any signs or symptoms of infection. Herpes simplex virus (HSV) causes is the virus that can cause cold sores (oral/nasal) or genital rash. HSV is contracted by skin-to-skin contact with someone who already has the virus, even if they do not have the rash showing at the time of contact. Deucravacitinib does not cause HSV, but it can lower your body's ability to defend against HSV and it may decrease your body's ability to prevent and HSV rash if you have been exposed in the past and carry the virus.

Hypersensitivity

As with any drug, hypersensitivity reactions can occur with patients taking deucravacitinib, and it is impossible to predict who this may happen to. These can range from a mild to severe. In the larger studies called Phase 3 trials, there were few events of hypersensitivity associated with taking deucravacitinib.

Malignancy (Cancer)

In the Phase 2 studies, there was 1 case of malignancy (malignant melanoma in situ, Grade 0) that was reported on skin biopsy on Day 96. The event was considered mild and nondrug-related by the investigator. In the larger Phase 3 trials, malignancies were rare and most events were considered not related to deucravacitinib use, or it was unclear if deucravacitinib played a role in the malignancy development.

Live Vaccine Risks: Live vaccines should not be given while you are taking deucravacitinib. Let all of your doctors know you are in a trial and receiving deucravacitinib before receiving any vaccine.

B6. RECRUITMENT AND CONSENT PROCEDURES**Recruitment**

Dermatologists from Beth Israel Deaconess Medical Center will be informed using IRB approved recruitment letters of this study and asked to refer eligible patients to our research unit. These letters will explain the purpose of the research, including a brief description of the nature and extent of involvement, and the investigator's email and phone number will be included.

In order to address the issue of patients feeling pressured to participate, a standard approach was developed and implemented years ago. This gives the patient the opportunity to actively demonstrate their interest before enrolling in the study. If a discussion about the study presents itself during a clinical encounter, the patient is offered to take the consent home and read and then asked to follow up with the clinic if they are interested. It is also attempted to have a physician who is not involved in their clinical care go over their consent form in order to provide further separation.

Informed Consent

Prior to entering the study, a licensed physician investigator will explain to the potential subject the nature of the study, its purpose, procedures, expected duration, and the benefits and risks involved in study participation.

Subjects will be given the opportunity to ask questions and be informed of their right of study withdrawal. After this explanation and before any study-specific procedures have been performed, the potential subject may voluntarily sign and date the informed consent form, thereby giving permission for the subject to enter the study.

Prior to participation in the study, the subject will receive a copy of the signed and dated written informed consent form and any other written information provided to the subject. If, for any

reason, the subject desires more time to consider the decision, the subject will be given a copy of the unsigned consent form for reference and instructed to call the office if they decide to participate in the study.

B7. STUDY LOCATION

Privacy

Subject visits will be conducted in the CRC at BIDMC or, rarely, in private patient exam rooms in the dermatology clinic if the CRC is not available at the time of subject visits. Both locations should ensure adequate privacy for patients. Patients will complete all study related procedures in these private settings, including questionnaires. Questionnaires will be in written form and returned directly to the investigators or study staff.

Pre-screening telephone calls and subject visits will be limited only to the minimum amount of data necessary to accomplish the research purposes. No sensitive questions will be discussed by telephone

Physical Setting

Subject visits will be conducted in the CRC at BIDMC or, rarely, in private patient exam rooms in the dermatology clinic if the CRC is not available at the time of subject visits. Both locations should ensure adequate privacy for patients. Patients will complete all study related procedures in these private settings, including questionnaires.

B8. DATA SECURITY

Data and Safety Monitoring

The study will be monitored by the principal investigators and members of the study staff. Given the short duration of the study and the low risk associated with these treatments, no Data Safety Monitoring Board will be convened. All data relevant to the assessments outlined in this protocol will be recorded in the case report form (CRF) and the subject's sourcebook.

Substantive changes in the protocol include alterations that affect the safety of subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, doses, assessment variable(s), the number of subjects treated, or the subject selection criteria. If needed, these changes will be initiated via formal written protocol amendment. This protocol amendment must be reviewed and approved by BIDMC CCI/IRB prior to implementation. If a protocol amendment results in changes to the informed consent form, the revised form must be approved prior to implementation by the sponsor as well.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject, and that are deemed crucial for the safety and well being of that subject, may be instituted for that subject only. Although these departures do not require pre-approval by BIDMC CCI/IRB, BIDMC CCI/IRB must be notified in writing according to specified guidelines after the departure has been made. Furthermore, the investigator will

document in the subject's case report form the reasons for the departure from the protocol and the ensuing events.

Regarding report to BIDMC CCI/IRB, the investigator will make accurate and adequate written progress reports to BIDMC CCI/IRB at appropriate intervals, not exceeding one year. The investigators will make an accurate and adequate final report to BIDMC CCI/IRB within three months after completion or termination of the study. The investigators will immediately make an accurate and adequate special report to BIDMC CCI/IRB for any serious adverse experience per IRB reporting policies.

The primary investigators will review all safety reports at their respective sites, and their findings will be forwarded to the BIDMC CCI/IRB.

Ethics Review

This study will be conducted according BIDMC CCI/IRB guidelines after approval by the BIDMC CCI/IRB.

Quality Control

This study will be monitored by the principal investigator, by members of the study staff, and by monitors/auditors form the BIDMC QI program, if needed. All data relevant to the assessments outlined in this protocol will be recorded in the case report form (CRF).

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☒ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☒ No

B10 Dissemination of Research Results

Subjects will be thanked for their participation in the study immediately following their last visit. Because we are not able to anticipate the final completion date of the study, which may take years, and because we are not primarily responsible for analyzing and publishing the data, it will not be feasible for investigators to provide results to individual subjects. Subjects may contact the PI following their completion of the study to inquire about the final findings of the study, if available to the investigators, at that time.

Planned dissemination of research results may include abstract presentations at dermatology conferences and submission of data for publication in academic journals as an original research article.

Plans for Disseminating and Communicating Study Results

When the study is completed a report will be written. This report will contain a description of the objectives, the methodology, the results and the conclusions of this study. The results of this study may be published by any one of the investigators, participating physicians or study staff after agreement with the PI.